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No. 84-290

IN THE

Supreme Court of the United States

OCTOBER TERM, 1984

ORTHO PHARMACEUTICAL CORPORATION,
Petitioner,

v.

CAROL LYNN WOODERSON,
Respondent.

On Petition for a Writ of Certiorari To the Supreme Court of the State of Kansas

MOTION FOR LEAVE TO FILE BRIEF AMICUS CURIAE AND BRIEF AMICUS CURIAE OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION IN SUPPORT OF PETITION FOR A WRIT OF CERTIORARI

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September 19, 1984

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MOTION OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION FOR LEAVE TO FILE BRIEF AMICUS CURIAE

The Pharmaceutical Manufacturers Association respectfully moves for leave to file the attached brief amicus curiae. The consent of the attorney for the petitioner has been obtained and filed with the Clerk, but respondent has refused consent.

PMA is a voluntary nonprofit association of 135 companies that are responsible for discovering, developing, manufacturing, obtaining Food and Drug Administration approval of, and selling almost all of the pioneer prescription new drugs in this country. Members of the association distribute prescription drugs, including oral contraceptives, in interstate commerce for sale throughout the country. These companies are subject to the new drug approval requirements and drug labeling

requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. §§ 301-392, and regulations issued thereunder by the FDA, 21 C.F.R. Parts 200-202, 300-361.

The decision of the Supreme Court of Kansas that petitioner Ortho Pharmaceutical Corporation asks this Court to review imposes punitive damages upon a pharmaceutical company on the ground that the labeling of the company's oral contraceptive product did not adequately warn of certain risks, even though the FDA did not include those warnings in the uniform labeling that it had written and prescribed for all oral contraceptives during the relevant time, and even though the FDA had refused to approve another manufacturer's requests to add the warnings to the labeling for its oral contraceptive products. The FDA is the federal agency charged by Congress with ensuring that the use of prescription drugs will be "safe" and "effective" under the conditions set forth in their labeling.

In subjecting the petitioner to liability for punitive damages, the Kansas Supreme Court has effectively imposed a state regulatory requirement for the labeling of oral contraceptive products, and has done so in a manner that frustrates a pervasive system of federal regulation of labeling for oral contraceptive products. The decision also imposes an enormous penalty, in the amount of $2.75 million in punitive damages, upon a pharmaceutical manufacturer for the very reason that the company's labeling from 1970-1974 consisted of the uniform labeling that was carefully considered and precisely written by the FDA, and from 1975 consisted of the uniform labeling with certain modifications approved by the FDA consistent with the product's "new drug" license.

On many other occasions and in many other cases, PMA has acted vigorously to protect the rights of its member companies and to express its views on important issues relating to federal regulation of prescription new drugs. PMA believes that the attached brief amicus curiae can make a contribution to the Court's decision whether to grant the petition for a writ of

certiorari in this case. PMA's amicus brief supplements and does not repeat the arguments presented in the petition for a writ of certiorari. The brief documents the pervasive federal regulation of drug labeling in general and the unusually active role of the FDA in prescribing labeling requirements for oral contraceptive products in particular. As PMA shows, the Kansas Supreme Court's decision imposing a state standard for oral contraceptive labeling is totally inconsistent with the federal regulatory scheme.

Accordingly, PMA moves for leave to file the attached brief amicus curiae.

Respectfully submitted,

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INTEREST OF AMICUS CURIAE

The interest of amicus curiae Pharmaceutical Manufacturers Association in this case is described in the foregoing motion for leave to file. This brief is concerned only with the first question presented by the petitioner.

STATEMENT

The first oral contraceptive was approved for sale as a "new drug" by the federal Food and Drug Administration (FDA), under a "new drug application" (NDA) submitted to the agen-

cy, in June 1960.[1] After a few years, the FDA received reports that this oral contraceptive might be associated with certain thromboembolic conditions. Accordingly, throughout the 1960s, the FDA undertook close surveillance of adverse effects reported from the use of these products.[2]

Details of the FDA's surveillance of oral contraceptive effects and the resulting prescription by the agency of the labeling that must accompany oral contraceptive products are set forth in the Argument section (Part II). In brief summary, so far as pertinent to the decision below—that petitioner Ortho should have included in the labeling of its products warnings of possible effects of the drug in addition to those prescribed by the FDA—the facts are:

The FDA established uniform labeling for oral contraceptive products in 1967 and issued revised uniform labeling in 1968.[3] Labeling is a term of art in drug law. Insofar as prescription drugs are concerned, it refers not simply to the actual label on the bottle of pills that a patient buys from a pharmacist but to all written material supplied to prescribing physicians by drug manufacturers.[4] It also includes, as in the case of oral contraceptives beginning in 1970, pamphlets written in lay language to be given by a physician to the patients for whom he prescribes a drug (often called "patient package inserts").

In December 1969, when it was considering revising the uniform labeling for oral contraceptives, the FDA learned that the British Committee on Safety of Drugs had advised practi-

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[1] "Competitive Problems in the Drug Industry": Hearings Before the Subcomm. on Monopoly of the Senate Select Comm. on Small Business, 91st Cong., 2d Sess., Pt. 16, at 6787 (1970) (hereafter "Nelson Hearings")(App. B, 32a). Pertinent parts of these Hearings are reproduced in Appendix B to this brief.

[2] Nelson Hearings 6787-88 (App. B, 31a-34a).

[3] Nelson Hearings 6788 (App. B, 33a-34a). The text of the 1968 uniform labeling appears in Appendix C to this brief.

[4] As defined by the statute, the term "labeling" includes all printed matter (1) upon the article or its container or (2) accompanying the article. 21 U.S.C. § 321(m). *See* 21 C.F.R. Parts 201, 202.

tioners to prescribe only products containing 0.05 milligrams (mg) or less of estrogen.[5] This committee acted on reports suggesting a relationship between the amount of estrogen in oral contraceptives and the incidence of thromboembolic disorders. The FDA considered the British report and action but deliberately did not include any mention of it in the revised uniform labeling for oral contraceptives that the agency issued in early 1970.[6] The FDA discussed the British report in a letter to physicians enclosing the revised labeling and said that it was planning studies to evaluate the accuracy of the findings.[7] Later that year the FDA specifically denied a request by an oral contraceptive manufacturer for permission to depart from the prescribed uniform labeling and include a reference to the British report and the comparative safety of higher and lower estrogen doses.[8] The FDA likewise did not include any reference to the British report when it prescribed a uniform patient package insert for oral contraceptives in June 1970.[9]

In 1974 and 1975, further studies confirmed the earlier finding that higher-dose estrogen products were associated with an increased incidence of thromboembolism.[10] Accordingly, Ortho (and some other companies) asked the FDA to approve the inclusion of a statement about this association in the labeling for their oral contraceptive products. The FDA approved Ortho's request to make this addition to its labeling in 1974, pursuant to a "supplemental" NDA, the agency's procedure for modifying the labeling of a drug that is subject to an NDA, 21 C.F.R. § 314.8.

Later, in December 1976, the FDA revised the uniform labeling for oral contraceptive products to include a statement

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[5] Nelson Hearings 6792 (App. B, 40a).

[6] Nelson Hearings 6792 (App. B, 40a-41a).

[7] The 1970 uniform labeling and "Dear Doctor" letter are reproduced in Appendix D to this brief.

[8] *See* Petition for a Writ of Certiorari, p. 7.

[9] 35 Fed. Reg. 9001 (June 11, 1970).

[10] *See* 41 Fed. Reg. 53630, 53635, 53638(ref. 3) (December 7, 1976).

that data from epidemiological studies "have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism," and a recommendation that new users of oral contraceptives should be started on lower estrogen-dose products.[11]

In this revised uniform labeling, the FDA also added a statement, in the adverse reactions section, that impaired renal function had been "reported in users of oral contraceptives, and the association [with contraceptive use] has been neither confirmed nor refuted."[12] Some of these reports included references in the medical literature to a rare kidney disorder called hemolytic uremic syndrome (HUS). Although the FDA was aware of reports about HUS,[13] it did not include any mention of this alleged side effect in its December 1976 uniform labeling for oral contraceptives. Even in 1982, when G.D. Searle & Co. requested approval from the FDA to include HUS as an adverse reaction on the labeling of its oral contraceptive products, the FDA denied approval.[14] In the agency's judgment, the criteria for including HUS as an "adverse reaction" in the labeling had not been met, even by 1982, because the reports of HUS were anecdotal, not based on well-controlled scientific studies in accordance with the statute and regulations. (*See infra* pp. 12-13)

From the fall of 1972 until June 1976, respondent Carol Lynn Wooderson took Ortho-Novum 1/80, an oral contraceptive

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[11] 41 Fed. Reg. 53630, 53634 (December 7, 1976) (revised labeling required by April 6, 1977); 43 Fed. Reg. 4223 (January 31, 1978) (additional revisions and final rule).

[12] 41 Fed. Reg. at 53638.

[13] *See* Petition for a Writ of Certiorari, p. 18.

[14] *See* Petition for a Writ of Certiorari, pp. 13, 18. Searle nonetheless persisted in the use of labeling for its products that included a statement about a possible association between HUS and the use of oral contraceptives. After Searle submitted additional information to the agency and requested reconsideration of the matter, the FDA in 1983 approved inclusion of HUS as an adverse reaction in the labeling of Searle's products. Searle's inclusion of an HUS statement in the labeling pending a final decision by the FDA to approve or reject the revised labeling is authorized by 21 C.F.R. § 314.8(d).

(0.08 mg estrogen) manufactured by petitioner Ortho. The labeling of petitioner's product from 1970 through 1974 consisted of the uniform labeling prescribed by the FDA in 1970. After 1974 it consisted of the uniform labeling plus a statement about a possible association between estrogen dose and increased risk of thromboembolism, a modification of the uniform labeling that was approved by the FDA under the federal "new drug" license for the product. In July 1976, Mrs. Wooderson was diagnosed as suffering from renal (kidney) failure and HUS.

After trial in a state court, the jury returned a verdict and the court entered a judgment for respondent and against petitioner Ortho for compensatory damages of $2 million and punitive damages of $2.75 million. The punitive damage award was based on Ortho's failure to warn in the product labeling that there was a risk of HUS from contraceptive use and, in the product labeling from 1970-1974, that higher-dose estrogen products had been found by the British Committee to be associated with a higher incidence of thromboembolic disorders.

The Supreme Court of Kansas upheld both the compensatory damages and the punitive damages awards. (App. A to the Petition.) The court upheld the imposition of punitive damages even though the FDA had not prescribed HUS or estrogen-dose warning statements for the uniform labeling of oral contraceptive products, and indeed had explicitly declined to authorize the inclusion of an HUS warning as late as 1982.

SUMMARY OF ARGUMENT

This case gives the Court an opportunity to decide an important question of federal law grounded in the Supremacy Clause of the Constitution and the comprehensive scheme for regulation of prescription new drugs in the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. §§ 352, 355. The decision below ignores that scheme and the FDA's singularly painstaking and detailed enforcement of it in its licensing and regulation of oral contraceptive products. The Kansas court premised an award of punitive damages on the failure to give warnings that

the FDA determined should *not* be included in the labeling of oral contraceptive products during the relevant time periods. The case thus poses issues that flow from this Court's recognition last term in *Silkwood* v. *Kerr-McGee Corp.*, 104 S. Ct. 615 (1984), that state tort remedies are subject to federal preemption if in their effect of prescribing standards that must be adhered to at the risk of being penalized by an award of punitive damages they conflict with federal law or stand as an obstacle to the accomplishment of Congressional objectives.

As an incident of its new-drug licensing authority, the FDA wrote uniform labeling to accompany oral contraceptives and approved modifications of the uniform labeling only when it believed that scientific evidence supported the addition of certain warnings or other statements to the labeling of such products. Fully aware of the studies that the Kansas court has decided should have been the subject of further warnings by petitioner, the FDA during the relevant time periods declined to require or approve the inclusion of such warnings in the labeling because the dangers were not substantiated. This action reflects the FDA's policy that to warn of unsubstantiated dangers is to risk obscuring real dangers in a mass of verbiage. The warnings that the Kansas court demands thus could not have been given by petitioner without the FDA's approval, consistent with the FDA's new-drug license for petitioner's oral contraceptive product and the agency's rules, and the Kansas court's insistence that they be given stands to thwart the FDA policy of stringent regulation of the labeling for oral contraceptives.

ARGUMENT

The decision below presents the important federal question whether punitive damage awards premised on a drug manufacturer's failure to give warnings that the responsible federal agency has not required or permitted in the federally prescribed or approved labeling of a drug (1) conflict with the comprehensive federal regulation of prescription drug labeling

and (2) frustrate the objective of the federal agency in establishing stringent regulation of the labeling for a particular class of drug products.

The Kansas Supreme Court authorized the imposition of punitive damages on the ground that the labeling of the manufacturer's oral contraceptive drug product did not contain certain label warnings, even though the warnings required under the state court's decision had been specifically rejected by the federal Food and Drug Administration during the relevant time periods. In refusing to defer to the federal regulatory scheme, the Kansas state courts have allowed the judgment of a lay jury to be substituted for that of the expert federal agency charged with ensuring that drug labeling contains the necessary information for the safe and effective use of drugs by consumers. This result conflicts with principles announced in prior decisions of this Court.

Last term, in *Silkwood* v. *Kerr-McGee Corp.*, 104 S. Ct. 615 (1984), this Court sustained an award of punitive damages under state tort law against a claim of preemption. In doing so, the Court nevertheless recognized that state tort remedies, including especially the remedy of punitive damages—the functional equivalent of regulatory fines for conduct that falls short of a regulatory prescription[15]—enjoy no special immunity from federal preemption. *San Diego Building Trade Council* v. *Garmon*, 359 U.S. 236 (1959). State tort remedies cannot validly be applied in respect of the subject of federal regulation when Congress has acted to displace state regulation by occupying a field, when state law "actually conflicts with federal law, that is, when it is impossible to comply with both state and federal law," or when "the state law stands as an obstacle to the accomplishment of the full purposes and objectives of Congress." 104 S. Ct. at 621. In *Silkwood* the company's only claim that was even colorable rested on occupation of the field, and that claim was refuted by Congress' manifested understanding that state tort remedies were available to victims of

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[15] *See* 104 S. Ct. at 625-26 (opinion of the Court); *id.* at 629-30 (dissenting opinion of Blackmun, J.); *id.* at 635 (dissenting opinion of Powell, J.).

nuclear accidents. *Id.* at 623-24. So far as the other possible bases of preemption were concerned, in *Silkwood* adherence to both a state and a federal standard of nuclear safety was not at all impossible even if the state standard was more demanding than the federal standard, and the imposition of a higher state standard did not stand in the way of the accomplishment of Congress' safety purposes and objectives but rather would serve them. *Id.* at 626.

In this case, to the contrary, apart from occupation of the field by pervasive federal regulation of prescription drugs marketed in interstate commerce, the kind of label warnings required by the Kansas court's decision had been specifically rejected by the FDA. Any oral contraceptive product "labeled" with any warning other than the warnings approved under the FDA's regulations would have been misbranded in violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 331(a), 352(f), 355(e). It was therefore impossible for petitioner to comply with both the Kansas and the federal law concerning label warnings. Additionally, the Kansas law of drug label warnings presents a serious obstacle to the accomplishment of the federal objective of licensing and regulating the labeling of oral contraceptive products in the interest of the safety of their users.

I. The Federal Food, Drug, And Cosmetic Act And The Regulations Promulgated Under It Establish A Pervasive Federal System Of Rules To Govern Prescription Drug Labeling.

A. The Federal Food, Drug, and Cosmetic Act Establishes a Comprehensive Federal Scheme Regulating the Approval and Labeling of Prescription New Drugs.

The heart of the federal authority to regulate prescription drugs in the interest of safety lies in the provisions of the Federal Food, Drug, and Cosmetic Act dealing with new drugs. The Act prohibits the marketing in interstate commerce of a new drug, as defined in Section 201(p), 21 U.S.C. § 321(p), unless a new drug application (NDA) has been filed

for the drug and approved by the FDA under Section 505 of the Act, 21 U.S.C. § 355.[16] Generic copies of a previously approved pioneer new drug individually require their own approved NDAs.[17] This process of product licensure necessarily entails extensive agency involvement in the labeling of new drugs as well as in assessing their safety and effectiveness.[18] The FDA exercised this licensure authority when it approved the marketing of oral contraceptive drug products.

Section 505(b) of the Act specifies the information that must be submitted as part of an NDA. In addition to safety and effectiveness data, an NDA must contain "specimens of the labeling proposed to be used for such drug." 21 U.S.C. § 355(b). Section 505(d) empowers the FDA to approve an NDA only if the drug has been shown to be safe and effective "under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof . . .." 21 U.S.C. § 355(d)(5). Furthermore, the FDA must disapprove an NDA if, "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular." *Id.* § 355(d)(6).

Under the new-drug approval process, the FDA must weigh a drug's therapeutic benefits against the potential risks from its use.[19] The FDA's decision whether to approve an NDA "also involves composing labeling to restrict the conditions for use

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[16] Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); Ciba Corp. v. Weinberger, 412 U.S. 640 (1973); Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645 (1973); USV Pharmaceutical Corp. v. Weinberger, 412 U.S. 655 (1973).

[17] United States v. Generix Drug Corp., 103 S. Ct. 1298 (1983).

[18] To carry out its responsibility for ensuring that drugs are safe and effective, the FDA has promulgated an elaborate and complex set of regulations that define "new drugs," that govern the research and clinical investigations that must precede submission of an NDA, and that govern the submission, evaluation, and approval or disapproval of NDAs. 21 C.F.R. Parts 310, 312, 314, 320.

[19] "Drug Safety": Hearings Before the Subcomm. on Intergovernmental Relations of the House Comm. on Government Operations, 88th Cong., 2d Sess., Pt. 1, at 150, 153 (1964).

and thereby limit the risks of harm."[20] A former general counsel of the FDA has explained this process:[21]

> "The FDA not only decides whether a drug may be marketed, it also determines how it may be promoted and sold. The agency approves, and for practical purposes prescribes, the labeling that the drug must bear. . . . In this critical part of the approval process the FDA attempts to refine and articulate its initial weighing of hazards and benefits. It believes, and indeed tort law assumes, that the information conveyed by the labeling will effectively control the use of a drug and thereby limit risks and enhance benefits."

Licensing of the labeling is thus inherent in the FDA's licensing of the new drug.

In addition to using its licensing authority to prescribe drug labeling in advance, the FDA is responsible for regulating the labeling of prescription drugs once they are marketed. Section 502(f) of the Act requires that drug labeling must bear

> "(1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users . . .." 21 U.S.C. § 352(f).

If a drug fails to contain the required warnings, it is misbranded under the FD&C Act, thereby subjecting its manufacturer to potential civil and criminal penalties. *Id.* §§ 331-337, 352. Where information discovered after a drug is marketed indicates a need for additional warnings to physicians, the FDA will require changes in the approved labeling. If the labeling is not corrected within a reasonable time, the FDA is empowered to withdraw the NDA approval, thus revoking the license to market the drug. *Id.* § 355(e).

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[20] Merrill, *Compensation For Prescription Drug Injuries*, 59 Va. L. Rev. 1, 9 (1973).

[21] *Id.* at 11. The author is now dean of the University of Virginia Law School.

The FDA's function as the expert agency with primary jurisdiction over the resolution of all questions regarding the labeling of new drugs (and drugs in general) cannot be carried out if state courts, and indeed lay juries, are permitted to second-guess the scientific and policy decisions the FDA makes.[22]

B. The Food and Drug Administration Has Established a Comprehensive and Pervasive System of Drug Labeling Regulations.

Drawing on the authority of both the FD&C Act and the Fair Packaging and Labeling Act,[23] the FDA has established a comprehensive system of regulations to govern the labeling of drugs. The FDA's drug labeling regulations are detailed and particular. These rules govern as to all drugs such matters as the label declaration of the manufacturer or distributor, the use of National Drug Code numbers to identify manufacturers and products, adequate directions for use, statements of ingredients, prominence of required statements, use of lot control numbers, statements of identity, and statements of dosage.[24] Other rules govern specifically the content and format of labeling for human prescription drugs.[25] A specific rule governs potentially misleading statements in drug labeling.[26] Additionally, a series of regulations establish special labeling requirements for particular kinds of drug products.[27] In their application to prescription drugs, these requirements are in addition to those embodied in the FDA-approved NDA—the individual federal license described above that specifies in detail the manner in which a prescription drug must be manufactured and labeled.

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[22] *See* Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 653-54 (1973); Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 627 (1973); Ciba Corp. v. Weinberger, 412 U.S. 640, 643-44 (1973).

[23] 15 U.S.C. § 1451 *et seq.*

[24] 21 C.F.R. §§ 201.1, 201.2, 201.5, 201.10, 201.15, 201.17, 201.18.

[25] 21 C.F.R. §§ 201.56, 201.57.

[26] 21 C.F.R. § 201.6.

[27] 21 C.F.R. §§ 201.300-201.317.

Section 201.57 of the FDA's regulations is entitled "specific requirements on content and format of labeling for human prescription drugs."[28] This regulation specifies in detail the circumstances in which reported adverse effects that might be associated with the use of a drug constitute "adverse reactions" that must be listed under that heading in the drug labeling. 21 C.F.R. § 201.57(g). As defined in the regulation, "an adverse reaction is an undesirable effect, reasonably associated with the use of the drug." *Id.* The FDA has construed "adverse reaction" as follows:

> "That definition would not include unsubstantiated reactions, disease symptoms, or apparently undesirable effects coincidental to the use of a drug, because they would not be reasonably associated with the use of the drug. . . . Accordingly, adverse effects and adverse experiences are not synonymous with adverse reactions and should not be included in prescription drug labeling." 44 Fed. Reg. 37434, 37453 (June 26, 1979).

Section 201.57 also governs the circumstances in which an adverse reaction rises to the level of a serious hazard that must be listed in the "warnings" section of the labeling. 21 C.F.R. § 201.57(e).

Where label statements are required under these standards, they must be made "in clear and unambiguous terms."[29] It was to ensure clear and concise warnings about *documented* hazards that the FDA promulgated its regulations requiring a specific format and content for prescription drug labeling:

> "[T]he law requires labeling to include warnings about both potential and verified hazards. Moreover, the law permits labeling statements with respect to safety only if they are supported by scientific evidence and are not false or misleading in any particular . . ..
>
> "Accordingly, labeling is not intended to be a dispositive treatise of all possible medical opinion about a drug. It is, instead, intended to advise about potential hazards and

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[28] This regulation is set forth in full in Appendix A to this brief.

[29] 39 Fed. Reg. 33229, 33231 (September 16, 1974).

convey documented statements with respect to safety and effectiveness." 40 Fed. Reg. 28582, 28583 (July 7, 1975).

When the available scientific evidence documents a reasonable association between the use of a drug and an adverse effect, the FDA requires the inclusion of that information in the drug labeling. If that required information is not included in the labeling, the FDA will not approve an NDA and the labeling for a new drug or will take regulatory action against a drug already on the market on the ground that it is misbranded under the Act. On the other hand, the FDA has determined that, when the scientific data do not document a "reasonable association" between the use of a drug and an adverse effect, such adverse effect "should not be included in prescription drug labeling." 44 Fed. Reg. at 37453.

The reason for this rule is obvious: If drug labeling contains too much information, it is less likely that any of the information will be absorbed by the prescribing physician.[30] A diffusion of warnings "would result in such uncertainty and confusion that the usefulness of such warnings in protecting the public against possible harm would be severely undermined, if not destroyed."[31] That is why a manufacturer must obtain the FDA's approval to include on a prescription drug "label" (or in other communications to physicians about the drug[32]) warnings about possible adverse effects that it knows about from experience or the literature, and why the FDA will not grant such approval if no "reasonable association" between the effect and use of the drug has been established.[33]

In keeping with these principles, the FDA has also issued regulations governing the circumstances in which comparative statements concerning safety of similar drug products may be made. Before drug labeling may include any statements comparing the relative safety, "either greater or less," of simi-

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[30] *See* 44 Fed. Reg. at 37453; 40 Fed. Reg. at 28583.

[31] 40 Fed. Reg. at 28583.

[32] 21 C.F.R. § 202.1.

[33] 21 C.F.R. § 314.8 (governing submission of a supplemental NDA by the manufacturer to propose and obtain approval of revised labeling).

lar drug products—such as the relative safety of high and low estrogen-dosage forms of oral contraceptive products—the statements must be supported by reliable scientific evidence. 21 C.F.R. § 201.57(c)(3)(v). Again, the purpose of this regulation is to avoid giving physicians erroneous or incomplete information concerning drug products.[34]

Despite this pervasive federal regulatory scheme, the Kansas Supreme Court has now authorized lay juries to substitute their judgment for that of the FDA in requiring, through the imposition of punitive damages, the inclusion in drug labeling of warnings of adverse effects that the FDA expressly determined to exclude from such labeling. It is inconceivable that 50 individual states can pick and choose among the rules that make up this comprehensive federal drug labeling scheme, or can require warnings based on the decisions of lay juries that are in addition to the warnings and labeling required by the expert federal agency, without interfering with the purpose of the federal drug law. Because state standards that impose drug labeling requirements that have been rejected by the FDA under federal law will frustrate the purposes of the FD&C Act, the federal requirements embodied in the FDA's labeling decisions must be given preemptive effect.

II. As An Incident Of Its New-Drug Licensing Authority Under The FD&C Act, The FDA Determined Not To Prescribe Or Approve The Label Warnings That Were Required Under The Standard Established By The Kansas Courts, And Thus The State Standard Is Preempted.

The award of punitive damages against petitioner Ortho was based on the fact that the labeling for its oral contraceptive product did not contain (1) a warning that HUS was a possible but unconfirmed side effect from use of oral contraceptives and (2) a statement, from 1970-1974, that higher estrogen dosage products might be associated with an increased risk of thromboembolic disorders based on the results of a British epidemiological survey conducted in 1969. To authorize an

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[34] 44 Fed. Reg. at 37441.

award of punitive damages on this basis is to disregard the FDA's express determinations that the HUS warning and the estrogen dosage relationship to thromboembolic disorders should *not* be included in oral contraceptive product labeling during the periods at issue here. In the FDA's judgment at that time, the available scientific evidence did not substantiate their inclusion. The conflict with federal authority is especially egregious because the FDA took a particular interest in oral contraceptives, played an active role in the studies of possible side effects, and even composed uniform labeling for oral contraceptive products.

The history of the agency's actions with respect to oral contraceptives was detailed by FDA Commissioner Edwards in 1970 before the Subcommittee on Monopoly of the Senate Select Committee on Small Business.[35] In his testimony, Commissioner Edwards outlined the FDA's "continued surveillance of adverse reactions" from the time the first oral contraceptive was approved in June 1960 through the British Committee's report on a suspected relationship of estrogen dosage to increased thromboembolic disorders in 1970, the report that the Kansas court considered crucial in imposing punitive damages upon petitioner.

The FDA's expert Advisory Committee on Obstetrics and Gynecology reviewed available scientific evidence on adverse effects of oral contraceptives and reported its conclusions to the agency in 1966 and again in 1969. The FDA funded studies of the effects of oral contraceptives on renal function, blood coagulation mechanisms, and other potential effects, including a study to determine the possible relationship of oral contraceptive use to thromboembolic disease.[36] The FDA established uniform physician labeling for all oral contraceptives in 1967 and monitored the labeling closely, revising it in 1968 and 1970. In 1970 it devised the concept of a "patient package

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[35] Nelson Hearings 6779-6837 (App. B). The pertinent parts of the testimony by Commissioner Edwards and Dr. Jennings of the FDA are set forth in Appendix B to this brief and summarized in the text.

[36] Nelson Hearings 6788 (App. B, 33a).

insert," which would provide information about risks and benefits of oral contraceptives in lay language directed to the user.[37] This was the first time that labeling directed to consumers had ever been required for an American prescription drug.[38]

In 1968, the results of epidemiological studies in Great Britain became available. After evaluating the data, the FDA concluded:

> "For the first time these studies demonstrated an increased incidence of thromboembolic disease in users of oral contraceptives. . . . Based on this conclusion, in June of 1968, FDA sent a letter to all physicians advising them of the British findings."[39]

Accompanying the FDA's 1968 "Dear Doctor" letter was the text of revised uniform labeling for oral contraceptives. That labeling contained information reflecting the results of the British studies.[40] The results of the British studies were confirmed by an American study published in August 1969. This study and other data regarding the use of oral contraceptives prompted the FDA in November 1969 to begin the process of changing the uniform labeling again.[41]

In December 1969, the FDA learned that the British Committee on Safety of Drugs had advised practitioners in that country "to prescribe only products containing .05 milligrams or less of estrogen."[42] This advice was based on reports suggesting the association of a higher incidence of thromboembolic disorders with oral contraceptive products containing .075 mg of estrogen or more. The FDA expressly determined not to include the British Committee report in the revised

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[37] 35 Fed. Reg. 9001 (June 11, 1970); 35 Fed. Reg. 5962 (April 10, 1970).

[38] "Regulatory Policies of the Food and Drug Administration": Hearing Before a Subcomm. of the House Comm. on Government Operations, 91st Cong., 2d Sess. 79 (June 9, 1970).

[39] Nelson Hearings 6788 (App. B, 34a).

[40] This letter appears in Appendix C to this brief. Source: Nelson Hearings, Pt. 17, 7022-25.

[41] Nelson Hearings 6792 (App. B, 39a).

[42] Nelson Hearings 6792 (App. B, 40a).

uniform labeling that it issued in 1970. Instead, the FDA decided to evaluate both the British data and the FDA's own data to determine whether the evidence justified a special warning or statement regarding products containing higher dosages of estrogen.[43] The FDA officials explained in their Congressional testimony that the process of evaluating the British data would be very complex, because it involved considerations of not only the safety of different estrogen dosages but also their effectiveness.[44] Thus, in the FDA's judgment, it would be inappropriate to single out products with more than .05 mg of estrogen for immediate regulatory action.

Accordingly, the FDA expressly decided *not* to include a warning or statement about a possible estrogen dosage relationship in the uniform labeling of oral contraceptive products in 1970. Instead, it notified prescribing physicians about the British Committee report by means of the "Dear Doctor" letter that accompanied the revised uniform labeling, and stated that the FDA was planning studies to determine the accuracy of the British finding.[45]

The uniform physician labeling required by the FDA in January 1970 therefore contained warnings about "an increased risk of thromboembolic disease associated with the use of hormonal contraceptives," but it did not include a statement about the British Committee's advice on low estrogen dosage products because any such statement would have the potential to mislead. Similarly, the FDA expressly refused to permit the drug manufacturer Searle to depart from the uniform labeling by adding a reference to the British report in the labeling for Searle's oral contraceptive products.[46] The FDA again declined

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[43] Nelson Hearings 6792 (App. B, 40a)(testimony of FDA Commissioner Edwards).

[44] Nelson Hearings 6793 (App. B, 41a-42a)(detailed explanation of the scientific and policy issues in the testimony of Dr. Jennings, Director of the FDA's Bureau of Medicine).

[45] The 1970 letter and revised uniform labeling appear in Appendix D. Source: Nelson Hearings, Pt. 17, 7017-21.

[46] *See* Petition for a Writ of Certiorari, p. 7.

to mention the British Committee's advice in June 1970 when it prescribed uniform patient labeling—the patient package insert—to inform users in lay language about the risks and benefits of oral contraceptives.[47]

The 1970 uniform labeling contained an adverse reaction statement about the possibility of increased blood pressure. The inclusion of this statement was based on the 1969 report of the FDA's Advisory Committee, concluding that this reaction had been established as occurring in users of oral contraceptives.[48] Although this report to the FDA mentioned the possibility of adverse effects on kidneys,[49] the FDA did not include such unsubstantiated effects in the 1970 uniform labeling. Nor were they included in the patient package insert required by the FDA later that year.

From 1970 through 1976, the FDA continued to conduct and fund studies of thromboembolic disorders, possible effects on kidney function, and other possible effects of oral contraceptives.[50] In 1975, the FDA issued press releases announcing new information on potential risks of oral contraceptives[51] and revised the patient package insert to include information about venereal disease.[52] In October 1975, the FDA also began to solicit comments on revised physician labeling for oral contraceptives.[53]

It was not until December 1976 that the FDA revised both the physician and patient labeling—required to be uniform for all oral contraceptive products, except for modifications approved by the FDA under the individual new-drug licenses—to include a statement that "epidemiological studies have

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[47] 35 Fed. Reg. 9001 (June 11, 1970).

[48] Nelson Hearings, Pt. 17, 6903. The Advisory Committee's Report is reproduced in Nelson Hearings, Pt. 17, 6839-6915.

[49] Nelson Hearings, Pt. 17, 6904.

[50] Nelson Hearings 6794 (App. B, 43a-45a)(discussing studies in progress).

[51] *See, e.g.*, "FDA Talk Paper," T75-67 (October 16, 1975).

[52] 40 Fed. Reg. 48918 (October 20, 1975).

[53] 40 Fed. Reg. 49813 (October 24, 1975).

shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism."[54] Even in this revised labeling, the FDA did not mention any association between the use of oral contraceptives and an increased risk of HUS. The omission of an HUS warning was significant. In its "continued surveillance" of adverse effects that might be associated with the use of oral contraceptives, the FDA knew of anecdotal reports of HUS in some users of oral contraceptives.[55] The agency believed that there was no evidence of a reasonable association between HUS and the use of oral contraceptives and, therefore, no HUS warning was required as a part of the uniform labeling. This remained the FDA's position in 1982 when it rejected a request by Searle to depart from the uniform labeling and include HUS as an adverse reaction in the labeling for Searle's products.[56]

Despite all this, the Kansas Supreme Court's decision holds that lay juries can substitute their judgment for that of the FDA with regard to the important scientific and policy decisions that underlie the content of drug labeling. The punitive damage award authorized by that decision will penalize a drug manufacturer who was *required by law* to conform the labeling for its oral contraceptive products to either the uniform labeling prescribed by the FDA or the uniform labeling with modifications approved by the FDA pursuant to its new-drug licensing authority under the FD&C Act. It is obvious that, if allowed to stand, the Kansas Supreme Court's decision will completely frustrate the purposes of the federal regulatory scheme and the FDA's especially close regulation of the labeling of oral contraceptive products.

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[54] 41 Fed. Reg. 53633, 53634 (December 7, 1976).

[55] *See* Petition for a Writ of Certiorari, p. 18. *See also* 21 C.F.R. §§ 310.300, 310.301 (requiring reporting to the FDA of studies and adverse drug experiences).

[56] *See supra* note 14.

CONCLUSION

For the reasons set forth above, the petition for a writ of certiorari should be granted.

Respectfully submitted,

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APPENDIX A

Specific Requirements On Content And Format Of Labeling For Human Prescription Drugs, 21 C.F.R. § 201.57

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Specific Requirements On Content And Format Of Labeling For Human Prescription Drugs, 21 C.F.R. § 201.57

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§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

Each section heading listed in § 201.56(d), if not omitted under §§ 201.56(d)(3), shall contain the following information in the following order:

(a) "Description":

(1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

(ii) The type of dosage form and the route of administration to which the labeling applies;

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for labels;

(iv) If the product is sterile, a statement of that fact;

(v) The pharmacological or therapeutic class of the drug;

(vi) The chemical name and structural formula of the drug;

(vii) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(2) If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated.

(b) "Clinical Pharmacology":

(1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and ac-

tions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information.

(2) Data that demonstrate activity or effectiveness in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this secton of the labeling only under the following circumstances:

(i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.111(a)(5)(ii) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.111(a)(5)(ii) of this chapter.

(c) "Indications and Usage":

(1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless the requirements is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless the require-

ment is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless this requirement is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter.

(d) "Contraindications": Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use

of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) "Warnings": Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

(f) "Precautions": Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) General: This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precau-

tions not required under any other specific section or subsection of the labeling.

(2) Information for patients: This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information required under this chapter to be distributed to the patient shall be referenced under the "Precautions" section of the labeling and the full text of such patient information shall be reprinted at the end of the labeling.

(3) Laboratory tests: This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy.

(4)(i) Drug interactions: This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the "Dosage and Administration" section of the labeling rather than under this subsection of the labeling.

(ii) Drug/laboratory test interactions: This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) Carcinogenesis, mutagenesis, impairment of fertility: This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information shall be included under the "Warnings" section of the labeling. Also, under "Precautions," the labeling shall state: "See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility."

(6) Pregnancy: This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information:

(i) *Teratogenic effects.* Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category:

(a) *Pregnancy category A.* If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category A. Studies in pregnant women have not shown that (*name of drug*) increases the risk of fetal abnormalities if administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. If this drug is used during pregnan-

cy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall also state: "Reproduction studies have been performed in (*kinds of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*)." The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(b) *Pregnancy category B.* If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling shall state: "Pregnancy Category B. Reproduction studies have been performed in (*kind(s) of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category B. Reproduction studies in (*kind(s) of animal(s)*) have shown *(describe findings)* at (*x*) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the

studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(c) *Pregnancy category C.* If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: "Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman only if clearly needed." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(d) *Pregnancy category D.* If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: "Pregnancy Category D. See 'Warnings' section." Under the "Warnings" section, the

labeling states: "(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(e) *Pregnancy category X.* If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Cagetory X. See 'Contraindications' section." Under "Contraindications," the labeling shall state: "(*Name of drug*) may (*can*) cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinant animal data.*) (*Name of drug*) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(ii) *Nonteratogenic effects.* Under this heading the labeling shall contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(7) Labor and delivery: If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and

the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) Nursing mothers:

(i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

(ii) If a drug is absorbed systematically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: "Because of the potential for serious adverse reactions in nursing infants from *(name of drug)* (or, "Because of the potential for tumorigenicity shown for *(name of drug)* in *(animal or human)* studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "Caution should be exercised when *(name of drug)* is administered to a nursing woman."

(iii) If a drug is absorbed systemically information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants

from *(name of drug)* (or, "Because of the potential for tumorigenicity shown for *(name of drug)* in *(animal or human)* studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when *(name of drug)* is administered to a nursing woman."

(9) Pediatric use: A specific pediatric indication, if any, shall be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage shall be stated under the "Dosage and Administration" section of the labeling. Statements on pediatric use of the drug for an indication approved for adults shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless this requirement is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter. If the requirements of § 314.111(a)(5)(ii) of this chapter cannot be met, this section of the labeling shall contain one of the following statements: "Safety and effectiveness in children have not been established," or "Safety and effectiveness in children below the age of (____) have not been established." If use of the drug in premature or neonatal infants, or in older children, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling; or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection of the labeling shall refer to it.

(g) "Adverse Reactions": An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same

pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to *(name of drug)* is (are) *(list reactions)*. This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are *(list reactions)*, which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are *(list reactions)*." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless this requirement is wavied under § 201.58 or § 314.111(a)(5)(ii) of this chapter.

(h) "Drug Abuse and Dependence": Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) Controlled Substance: If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) Abuse: This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

(3) Dependence: This subsection of the labeling shall describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details shall be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described.

(i) "Overdosage": Under this section heading; the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

(2) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis).

(3) Oral LD_{50} of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as

urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses.

(4) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening.

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) "Dosage and Administration": This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milli-

grams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

(k) "How Supplied": This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

(1) The strength of the dosage form, e.g., 10-milligram tablets, in metric system and, if the apothecary system is used, a statement of the strength is placed in parentheses after the metric designation;

(2) The units in which the dosage form is ordinarily available for prescribing by practitioners, e.g., bottles of 100;

(3) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code; and

(4) Special handling and storage conditions.

(l) "Animal Pharmacology and/or Animal Toxicology": In most cases, the labeling need not include this section. Significant animal data necesssary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) "Clinical Studies" and "References": These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the "Clinical Studies" or "References" section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for the use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under § 314.111(a)(5)(ii) of this chapter.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug.

(Secs. 502, 503, 505, 506, 507, 701, 52 Stat. 1050-53 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 352, 353, 355, 356, 357, 371); sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262))

[44 FR 37462, June 26, 1979]

APPENDIX B

Testimony (Partial) of FDA Commissioner Edwards Before The Subcommittee On Monopoly, Senate Select Committee On Small Business (March 4, 1970)

APPENDIX B

Testimony (Partial) Of FDA Commissioner Edwards Before The Subcommittee On Monopoly, Senate Select Committee On Small Business (March 4, 1970) (6779)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition In the Pharmaceutical Industry)

WEDNESDAY, MARCH 4, 1970

U.S. SENATE,
SUBCOMMITTEE ON MONOPOLY OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:35 a.m., in room 318, Old Senate Office Building, Hon. Gaylord Nelson (Chairman of the Subcommittee) presiding.

Present: Senators Nelson, McIntyre, and Dole.

Also present: Benjamin Gordon, Staff Economist; Elaine C. Dye, Clerical Assistant; James P. Duffy III, Minority Counsel; and Dennison Young, Jr., Associate Minority Counsel.

Senator NELSON. Our witness today is Dr. Charles Edwards, Commissioner, Food and Drug Administration.

Dr. Edwards, the committee is very pleased to have you appear here today. Your statement will be printed in full in the record.

You may present it as you desire, and if you wish to extemporize from it at any time, or elaborate on it, feel free to do so.

I assume you do not mind if we interrupt with questions as you go along.

Dr. EDWARDS. Not at all.

Senator NELSON. All right, go ahead, Doctor.

STATEMENT OF DR. CHARLES C. EDWARDS, COMMISSIONER, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. JOHN JENNINGS, DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; WILLIAM W. GOODRICH, GENERAL COUNSEL, FOOD AND DRUG ADMINISTRATION; AND DR. JOHN SCHROGIE, FOOD AND DRUG ADMINISTRATION

Dr. EDWARDS. Thank you, Senator Nelson, Senator Dole.

I would like to begin by introducing my colleagues. On my right, Dr. John Jennings, who is Director of the Bureau of Drugs, and on my left is Mr. William Goodrich, who is the general counsel for the Food and Drug Administration.

We certainly appreciate this opportunity to present to the committee the views of the Food and Drug Administration on some of the issues raised during these hearings. The primary issue, as we see it, has been the relative safety or oral contraceptives and a concern for public understanding of the risks associated with them. (6780)

We have, needless to say, carefully followed the progress of these hearings. You have heard a wide range of opinion concerning the safety of oral contraceptives. The opinions of these witnesses have been expressed intelligently and sincerely. They certainly merit serious consideration, both by you and by the Food and Drug Administration.

However, the expression of an informed opinion is not the same as making a decision. We, in the Food and Drug Administration, also have expert opinions; but it is our responsibility to study the available scientific data, consider the advice of our consultants and render a decision on the safety and efficacy of new drugs under the Federal Food, Drug, and Cosmetic Act.

At this point I wish to summarize the Food and Drug Administration's current position. I would like to emphasize

"current", because this is a situation that can change from month to month, year to year. However, our position is that the oral contraceptives are an effective and safe method of birth control, but as with other potent drugs there are both contraindications and complications.

Women whose history and present medical condition include thromboembolic disorders, impaired liver function, known or suspected cancer of the breast, estrogen dependent tumors, and abnormal bleeding should not take oral contraceptives.

Senator NELSON. Doctor, may I ask a question at this point?

Dr. EDWARDS. You certainly may.

Senator NELSON. On the use of the word "safe" in respect to the oral contraceptives, I think that there is considerable confusion within the medical profession and the public alike as to how the word "safe" was being used when the Hellman committee came to that conclusion and used the phrase "Safe within the intent of the law."

I would just like to read to you what Dr. Hellman said before the committee, and ask for your comment on it. I shall read out of context a couple of excerpts of his testimony.

This is Dr. Hellman speaking when he appeared before the committee—

> It is quite apparent if you read the report, in the first report the committee recognized certain very serious problems with oral contraceptives. They, however, were unwilling, and rightfully, I believe, to say these things ought to come off the market.

Now, I skip down further where Dr. Hellman states:

> Now, in discussing the Chairman's report, the second report, with the committee, I said to them that a more forthright statement has to be made. We cannot just hide behind rhetoric, we are going to have to say something and we have an option. These are not safe and then the commissioner might have to take them off the market, if you believe this. We can say these are safe, and our scientific data really did not permit that kind of statement.

I doubt whether one doctor in 10,000 in the country knows that this was what Dr. Hellman, the Chairman, said and understands the context within which the word "safe" was used in reaching the conclusion when the Chairman of FDA's Advisory Committee said "safe within the meaning of the intent of the law."

Would you mind elaborating on that? (6781)

Dr. EDWARDS. Certainly. In categorizing this drug as safe, I do not want to imply, by any stretch of the imagination, that this is an innocuous drug. It is a very potent drug, and when arriving at this decision to call it a safe drug we had to utilize the same standards we use for all other drugs.

As you well know, most of the other "safe" drugs, the powerful drugs, have certain contraindications. There are certain dangers in taking any drug, and they have to be taken under the conditions which are stated very clearly in the labeling.

So again, I would like to emphasize that in establishing this classification, we applied the same standards for the oral contraceptives as we have for all other drugs in categorizing them as safe.

Senator NELSON. The use in this context, then, was not in the ordinary dictionary use of the word—

Dr. EDWARDS. It certainly was not. It was a Food and Drug Administration description of the word "safe", which really is "safe under the conditions of labeling," and which perhaps is a more accurate definition.

Senator NELSON. This is a legal question. Dr. Hellman mentioned that he discussed the phrasing—do you have Dr. Hellman's phrasing?

In any event, he discussed how it should be phased with your counsel, Mr. Goodrich. Perhaps you may wish Mr. Goodrich to respond to this. But it raises another question of some significance, it seems to me.

Dr. Hellman said:

> Now, it therefore wrote the sentence that has caused you and Mr. Gordon and other people some difficulty. I take full responsibility for writing this sentence "safe within the intent of the legislation." But I did have consultation in writing the sentence.

And so forth, and he refers to your counsel, Mr. Goodrich.

If it had been my responsibility, I might have come to the same conclusion, but it does raise a question about the intent of the law and its meaning.

In 1938 Congress passed the statute requiring that to market a drug proof of safety must be submitted, adequate proof of safety or proof of safety acceptable to the FDA must be presented.

I would just like to ask Mr. Goodrich what he thinks was intended at that time. Let me state it this way:

In 1938 there were no oral contraceptives. In 1938, I would assume that the Congress was thinking of a drug for treatment of a specific target organism in a specific disease situation. In fact, it was in response to a particular safety problem that arose at that time respecting sulfanilamide, and maybe Mr. Goodrich will have a different view—and correct me if you do—that Congress was thinking then of a drug in which the issue was, is it safe for the particular disease situation which it is being used for, that is, the drug does have side effects, we are well aware of that; however, under the circumstance the illness of the patient indicates that on balance the risks of the side effects from the use of the drug are far outweighed by the benefits that the patient would get from the use of the drug for the particular disease situation that exists. (6782)

And just to delineate it a little further, let us take the case of chloramphenicol on which we had substantial hearings. This is a very potent drug and everybody knows it. It has in a certain incidence, some dramatic side effects involving blood dyscrasias, including aplastic anemia.

In today's circumstance, chloramphenicol, according to the National Research Council of the National Academy of Science, is not the drug of choice in any disease. It is the choice only when the target organism is subject to control by chloramphenicol, when no other drug will do the job, and when the disease situation is very serious.

So clearly, if you had some disease organisms that would not respond to treatment by tetracycline or any other drug, and the patient was seriously ill and the target organism was sensitive to chloramphenicol, the drug under that situation is safe within the meaning of the law.

However, if the disease is subject to treatment by tetracycline, it is not safe within the meaning of the law or if the patient has a serious disease or if the target organism is not subject to control by chloramphenicol, it is unsafe.

Is that your understanding of what the law means?

Mr. GOODRICH. Yes. My understanding is that all safety decisions have to be made in the context of the conditions for which the drug is prescribed, recommended or suggested.

Now, going back to what Congress had in mind in 1938 when they focused on an acute episode of poisoning, it happened to be due to the vehicle and not the drug itself. But as soon as we began passing on safety from the very first drug, the sulfanilamides, that were involved there, those drugs were not safe in any absolute sense of the term but they were quite safe in treating infectious disease at that time, because many of those were life threatening.

Now, in that class of drugs, of course, it is relatively easy to balance benefit-to-risk, which is the test here. But there are other types of drugs that we have had to deal with over the years, drugs used for prophylaxis, or that type of drug, and in each instance it is essential that the agency balance benefit to risk, because there are very few drugs that have no side effects whatever, if they do anything.

There are some innocuous drugs that do not do anything, but if they are innocuous, then they do not have any benefit or any risk; they are just ineffective.

But from the beginning of time we had to deal with the sulfanilamides, first as a class, with the corticosteroids, and many other classes of drugs that came on the market after 1938. And this was really kind of the beginning of a new era of chemotherapy that had both beneficial effects and side effects and contraindications that were necessary to be observed in using the drug.

Now, you had drugs effective against specific target organisms and effective as prophylactic measures.

Senator NELSON. Let me ask this question, though. Is it not correct when using the word "safe" that you do not mean safe in general, you mean safe for this particular patient who has a particular disease situation which the doctor decides that this drug will effectively treat, that is, target organism is subject to control by this drug, and on balance it is better that the patient risk whatever side effect this drug has rather than risk letting the disease run its course untreated by any drug. (6783)

It is an individual case, an individual disease, an individual prescription under an individual circumstance; is that not what we mean by "safe"?

Mr. GOODRICH. That is the decision for the individual prescriber, but the decision for the Food and Drug Administration has to take into account different circumstances in which the drug will be used, some in private practice, others in university medical centers.

It has to take into account the total experience with the drug in the total prescribing population, and make a judgment there on all of these circumstances, this drug will be reasonably safe, that is, its benefits outweigh its risk under the circumstances in which it enters the market.

There have been a few instances in which drugs were allowed to enter the market only for use in university-type

hospital settings, but in others the drug is permitted for widespread prescribing in most instance. But the Food and Drug decision has to take into account all of these circumstances in reaching a safety decision.

Senator NELSON. Maybe I am not making myself clear. When you say "safe within the meaning of the law" are you not saying that we mean safe for the appropriate use of that drug under an appropriate circumstance in a specific disease situation?

Mr. GOODRICH. Certainly.

Senator NELSON. Now, then, how do we bring the word "safe" to bear in the circumstance here of the oral contraceptive when: (1) There are alternative methods; (2) when, let us say, you are dealing with an intelligent, healthy, well-motivated prospective user? How does the word "safe" apply in that respect?

The person has available medical care and a good hospital, has a good physician, has all of the facilities of the medical profession available as contrasted with the situation in which the patient has diabetes, or the patient has a history of high blood pressure, or carcinoma in the immediate family, something like that. How do you evaluate that specific case, the healthy patient with the finest medical facilities available with respect to the phrase "safe within the intent of the law"?

Mr. GOODRICH. As you pointed out, that individual evaluation is for the prescriber, but as I approach it, as I see the responsibility of the Food and Drug Administration, it is to make sure that that prescriber has before him the information that is necessary for the safe, effective use of this drug.

Now, the drugs are essentially very effective. They have two classes of side effects, some troublesome, but not serious; some serious. Our role is to make sure that the material going from the sponsors of these drugs to the prescribers fully discloses both the benefits and the risk and that for the doctor to make a judgment there, after he has taken this lady's history,

after he has made the typical examination, the physical examination, and after he has taken into account all of the things that he is warned about, or cautioned about, or precautioned about, or contraindicated about in the labeling, to make the choice that this is a safe medication for this patient and that this is the one most likely to be effective. (6784)

Senator NELSON. If the patient is a healthy, well-motivated user, or prospective user, who could afford the best medical care, you do not have a problem of weighing the risk of a baby being born not in a hospital, but in a very poor circumstance. You are not weighing the question of whether the woman has psychological problems or diabetes, or disease; we are aiming at the problem of the perfectly healthy person.

Then under those circumstances, where there are alternative methods of birth control and we are dealing with the question of safety, is there any obligation by the doctor to disclose to that patient the benefits and side effects of this contraceptive versus those of alternative methods of contraception?

Dr. EDWARDS. I think there is an absolute responsibility of the physician to: (1) Point out the alternative methods of contraception, and the contraindictions to each, and then I think it is a judgmental consideration on the part of both the physician and the patient in arriving at an appropriate choice of contraceptive methods.

But certainly the physician has a primary responsibility, as we see it, in bringing this information on the safety of this particular product to the patient.

Senator NELSON. To the patient's attention?

Dr. EDWARDS. Right.

Senator NELSON. Because the situation is quite different if there is no disease problem, when there is no other problem.

Dr. EDWARDS. Absolutely.

Senator NELSON. The patient is entitled then to know the facts on thromboembolism or other risks, with a right then to

decide, along with the doctor, whether she would use an oral contraceptive or another device; is that right?

Dr. EDWARDS. Absolutely. And I would again emphasize that in our judgment this is a potent, powerful drug that has to be utilized under the supervision of a competent physician.

Senator NELSON. Then does not the Newsweek poll raise quite a dramatic problem nationwide, when it is your position as well as the position of the former Commissioner Dr. Ley, as well as many witnesses before the committee, that there should be disclosure to the user? Are we not confronted with a very serious situation when the Newsweek poll says that two-thirds of the women interviewed said they were told nothing about side effects?

Dr. EDWARDS. I think very definitely, yes. I think that, unfortunately, the subject of the oral contraceptive has become somewhat of an emotional one in the eyes of many women, in the eyes of the public generally.

I think one of the responsibilities of the Food and Drug Administration is to bring the facts to bear so that they are available to the patient. I think that there have been more women taking the pill than perhaps should have been taking the pill.

I am not sure that this number is absolute, but I think it does indicate there is a need to better inform the patient of the potential dangers of the pill and the risks involved. (6785)

Senator NELSON. If, as you and many others state, it is important to share the knowledge of the side effects with the user, what do we do about the fact that according to the Newsweek poll two-thirds of the doctors are telling the patients nothing about side effects?

Dr. EDWARDS. As I am going to suggest in my prepared testimony, Senator Nelson, I think that the Food and Drug Administration has a responsibility to make sure that these individuals taking the oral contraceptives have received this information, and this is what we are going to propose.

This is what we are planning to do immediately, as a matter of fact.

Senator NELSON. Excuse me. You are planning immediately to do what?

Dr. EDWARDS. We are going to publish in the Federal Register a patient information sheet that we are proposing be placed in all containers of oral contraceptives.

Senator NELSON. That are received by the user?

Dr. EDWARDS. By the user, right.

Senator NELSON. Has that ever been done with any other drug?

Mr. GOODRICH. Yes. There have been a few instances in which it was necessary to have the prescribing information with the package.

Senator NELSON. What drugs are they?

Mr. GOODRICH. Well, I think back—

Dr. JENNINGS. I do not think we have ever required it to the extent that is contemplated in this case. However, we have in at least one recent instance gone contrary to the traditional approach of requiring only the information the doctor wants on the dispense package of a prescription drug. In this instance, we required a warning directed to the patient in a certain class of drugs, the isoproterenol aerosol inhalants. The reasons they were somewhat comparable to what we are facing today, in that the drugs were prescribed in such a way that they could be refilled, the prescriptions could be refilled repeatedly, and the patient therefore had more control over the medication than they would with most prescription drugs.

So we did require a warning on the dispensed containers, directed to the patient.

Senator NELSON. What did the warning say?

Dr. JENNINGS. It simply warned against certain hazards here, associated with overdosage, and that if the usual or

desired effect of release of difficult breathing was not obtained, that the physician should be consulted.

That, of course, does not approach in scope what is contemplated with the oral contraceptives.

Senator NELSON. So this is the first time that you will be proposing that there be a user, so to speak, a user package insert that tells the patient something in detail about the drug?

Dr. EDWARDS. Certainly in the detail that we propose this one in, yes.

Senator NELSON. Will that be in all packages dispensed to the user?

Dr. EDWARDS. We visualize it being in all of the oral contraceptive packages, yes. (6786)

Senator NELSON. Well, I certainly want to commend you for moving in that direction. I had thought maybe there was a legal question, and I had had the counsel draft a bill to accomplish the same purpose, which we introduced yesterday, but which your action will make unnecessary.

Is there any legal problem about the authority of the FDA to require a user package insert?

Mr. GOODRICH. Not if a finding is made as to the product here that is necessary for the safe use of the drug. The legal point being raised, I suppose, has to do with the ordinary rule that prescription drugs dispensed to the user do not themselves carry the warning of hazards, but that information is normally directed to the physician himself, and the law requires that the package dispensed contain such warnings as the prescriber requires in his prescription.

In this case, upon a finding that this kind of information cannot be safely left to word of mouth, that it must be communicated in a more orderly way, this is a safety factor that enters into the new drug decision and can be required, in my opinion.

Senator NELSON. We missed that aspect of the law. I had assumed that it would take some additional legislation, but I am pleased to hear that it does not.

Pardon me for interrupting, Doctor. I had another question I might as well ask right now, because it comes within the next sentence of your prepared statement.

In reading your sentence below, the one we just discussed, "Women whose history and present medical condition include thromboembolic disorders, impaired liver function," as you were reading it, you inserted a "family history of diabetes." This is not in my text.

Dr. EDWARDS. No, I inserted it.

Senator NELSON. So it would read "impaired liver function, family history of diabetes"?

Dr. EDWARDS. Strong family history of diabetes.

Senator NELSON. "Known or suspected cancer of the breast."

This is the question we discussed yesterday with Dr. Cutler, in which he would use, I guess, about the same language you would as to diabetes. We asked him this question, whether the package insert which I believe uses the language "known or suspected cancer of the breast," whether that was adequate. He feels, if I recollect his testimony correctly, that it ought to say about what you said, about diabetes, but that if, as he put it, a sister, mother, or an aunt had cancer of the breast, it should be a contraindication.

Would you agree with that?

Dr. EDWARDS. No, I would not. I would not be quite that forceful in my statement. I think certainly there is an area that we have to keep a very careful eye on, but at this point in time I do not think that our information, our data, would substantiate a statement of that magnitude.

Senator NELSON. So you would not be inclined to even use the words "family history," as you do with diabetes?

Dr. EDWARDS. Not at this point in time. Again, this is one of those areas I think we have to watch very, very carefully, and very shortly we might have to add that.

(6787)

Senator DOLE. Mr. Chairman, we had a subsequent witness yesterday afternoon, Dr. Peterson, who is chairman of the Department of Obstetrics and Gynecology at the Washington Hospital Center, who had much the same indication, that he would not include the family history.

I might also say, Mr. Chairman, that later on in the statement we will be apprised fully of the knowledge of the leaflet that will become the insert. Is that correct?

Dr. EDWARDS. That is correct, yes.

Senator NELSON. Please proceed, Doctor.

Dr. EDWARDS. Thank you.

The risk of having thromboembolic disorders is four to nine times greater for users than for nonusers. Perhaps more accurately state, the mortality for users — I emphasize mortality — is approximately three women per hundred thousand versus 0.5 per hundred thousand in the nonusers. Consequently a few apparently healthy women taking this drug will be affected. For all women, an understanding of this risk and other less-serious adverse reactions will reduce the possibility of serious consequences.

In fact, I must say that the question of the safety of all contraceptives which has come out in these hearings can be clarified only through better public education as to what is involved.

I believe only one witness thus far has suggested to the subcommittee that oral contraceptives be taken off the market. What has been suggested, I think, is that the question of safety is directly related to understanding of risk. I certainly agree and I am prepared today to suggest how we can help the physician better inform his patients on the safe use of oral contraceptives.

First I would like to review the history of the Food and Drug Administration's action with respect to oral contraceptives.

The first oral contraceptive, a combination of mestranol and norethynodrel, was approved for sale in this country in June of 1960. During the next few years the Food and Drug Administration received increasing reports that this oral contraceptive was associated with certain thromboembolic phenomena. A committee of experts was formed by FDA to review and analyze available data and to determine if use of this oral contraceptive resulted in an increase in the incidence of thromboembolic conditions. The committee chaired by Dr. Irving S. Wright, reported in September 1963, that in their opinion no significant increases in the risk of thromboembolic disease had been demonstrated.

Less than 2 years later, in April 1965, the first two sequential products were approved. These new products stimulated wider interest in birth control through use of oral contraceptives.

It was estimated that during 1965 the average number of users of all marketed oral contraceptives in the United States had reached 5 million.

Although the Wright committee found no demonstrated increased risk, the Food and Drug Administration continued its surveillance of adverse reactions. An FDA Advisory Committee on Obstetrics and Gynecology was established under the chairmanship of Dr. Hellman. This committee was asked to consider all of the available evidence and to provide the Food and Drug Administration with the best possible advice. (6788)

This committee of experts issued their first report in August of 1966. They found no adequate scientific evidence at the time to say that these compounds were unsafe for human use. However, the committee noted their concern for better data and made several recommendations which were subsequently acted upon by the Food and Drug Administration.

Included among these were the following:

First of all, the funding of a retrospective study to determine the possible relationship of oral contraceptives to thromboembolic disease.

Second, to support prospective studies utilizing groups of subjects especially amenable to long-term follow-up.

Third, the continuation and strengthening of FDA surveillance system.

Fourth, review of the mechanism for storage, retrieval and analysis of oral contraceptive surveillance data.

Fifth, to support laboratory investigation on carbohydrate metabolism, lipid metabolism, renal function, blood coagulation mechanisms, and potential carcinogenic effects in animals and man.

Sixth, to establish uniform labeling of contraceptive drugs.

Seventh, discontinuation of time limitation for administration of contraceptive drugs.

Lastly, to expedite approval of low dosage oral contraceptives.

The retrospective study was initiated; uniform labeling was achieved; the 2-year limitation was dropped; computer improvements were made in the storage, retrieval, and analysis of surveilance data; better reporting was discussed with the manufacturers; and effects were made to obtain better reporting from hospitals and from prescribers.

By 1966 competition in the oral contraceptive market had resulted in exaggerated and misleading claims. Advertising to physicians and some promotion materials attempted to establish ideas of product superiority which in our judgment had no scientific basis.

As a result, the Food and Drug Administration's efforts to correct this situation led us to the uniform label approach for oral contraceptives.

By early 1968, the improved surveillance system was reporting increasing numbers of thromboembolic diseases associated with women taking the oral contraceptive. At about the same time results of epidemeological studies in Great Britain became available. For the first time these studies demonstrated an increased incidence of thromboembolic disease in users of oral contraceptives. The British data, compiled by Dr. Inman, Dr. Vessey, and Dr. Doll, were reviewed by our experts who also considered the available U.S. data. These experts concluded that there was "a definite association between the use of oral contraceptives and the incidence of thromboembolic disorders."

Based on this conclusion, in June of 1968, FDA sent a letter to all physicians advising them of the British findings.

Senator NELSON. How many cases of thromboembolic disorders had been reported to the department by the end of 1969? Do you happen to have that information? (6789)

Dr. EDWARDS. I would like to refer that question to Dr. Jennings, or a member of his staff.

Senator NELSON. On both deaths and morbidity.

Dr. JENNINGS. We have been compiling these on an annual basis for the past couple of years, and as of December 31, 1969, the total number of reported reactions for that period, July 1, to December 31, 1969, included 15 deaths and 28 nonfatal thromboembolic cases.

Senator NELSON. Over what period of time?

Dr. EDWARDS. From July to December. Is that not correct?

Dr. JENNINGS. That is right. That was for that particular year.

Senator NELSON. How many deaths?

Dr. EDWARDS. Fifteen.

Senator NELSON. And what was the other, thromboembolic?

Dr. JENNINGS. Yes, nonfatal thromboembolic, 28, with about six other miscellaneous adverse reactions.

Mr. DUFFY. Doctor, so I can understand these figures now, are these figures that are actually documented? In other words, it is clear that these are pill-related or are these just incidents which have occurred in people who have used the pill? You may or may not know.

Dr. JENNINGS. Deaths and the nonfatal. In fact, all of these adverse reactions are ones that we attribute to the use of the drug.

Mr. DUFFY. I would assume, then, that if you just looked at the gross number of deaths from thromboembolic accidents of women using the pill, there would be a larger number than 15?

Dr. JENNINGS. Yes, I am sure there would.

Mr. DUFFY. And you narrowed this down to instances where you could be sure it was pill-related?

Dr. JENNINGS. In attempting to establish a cause and effect relationship in any adverse reaction to a drug, where the adverse reaction is one that occurs for other reasons, but the linking of the two is extremely difficult. I think that we cannot always say with absolute certainty that a cause and effect relationship exists.

Now, therefore, even in our labeling, the retrospective studies, for instance, that were done, can establish only that; that they do not establish the precise cause and effect relationship.

We have here the tabulation that we do on these, and although I do not have handy the figure that I think the Senator was asking for, the total that we have to date, we can tabulate this fairly rapidly for you, if you want us to do that.

Senator NELSON. Do you want to submit it for the record?

Dr. JENNINGS. Yes, sir.[1]

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[1] See p. 682

Senator NELSON. I was getting at another aspect of this. We have had witnesses over the past 3 years, distinguished physicians, who deplored the state of reporting on various diseases as being wholly inadequate. By coincidence, last week we had an internist before the committee, who talked about the forms he had to fill out and that he used to religiously report but never got any playback from FDA — this was several years ago — and finally he stopped reporting entirely. (6790

I would like to ask your view about the status of reporting to the FDA on side effects, which you would like to know about. But first, let me read what Dr. Best said before the committee, about 2 years ago.

This is from a statement of William R. Best, chief, Midwest Research Support Center, Veterans Administration, Edward Hines, Jr. Hospital, Hines, Ill. He said:

> I am not sure how much effect the reporting system would have itself. It would produce a universal reporting system. . .that would have a little more meaning than those I have written about that I related to voluntary reporting.
>
> In other words, we would have a better feel for what the total number of cases are. I think we still would not have the whole picture.
>
> I know that in a recent study in Philadelphia, for example, five of the medical school affiliated hospitals tried to set up their own reporting system to catch all the adverse reactions occuring in all of these hospitals. People being people, the way they are, when they went back to check and see how complete their reporting system was, even though the chief of every service told all of his residents and internes to report every case that came through. I think they reported somewhere in the neighborhood of 5 percent. About 95 percent still did not get reported, even though this was the rule of the particular hospital.

This would seem to have been a case where there was a conscientious, specific effort, and according to Dr. Best, about 5 percent of the side effects were reported.

Do you think in your experience, in your judgment, that figure is anywhere near in the ball park of any kind of voluntary reporting the FDA gets on side effects?

Dr. EDWARDS. I do not think I am in a position to give you an absolute figure. I would say without any hesitation our reporting system is poor. As long as we continue to have a reporting system that is voluntary, as it is right now, where we have very little access to the medical records in both hospitals and in doctors' offices, I think the likelihood of our establishing a really accurate, up to date reporting system is not going to be very encouraging.

I think that we have to move in this direction for all drugs, not just for the oral contraceptives. I think a complete adverse reporting system has to be established in this country eventually, if we are really going to provide the surveillance for these powerful drugs that is necessary.

Senator NELSON. I bring this up just to make the point that if the Philadelphia study and the five hospitals with the chiefs of all the services cooperating produced only a 5-percent reporting result, all of your reports on the incidence of deaths and other side effects from the pill, would have to be multiplied by 20 get an accurate figure.

Dr. EDWARDS. I have some reservation as to whether this is an accurate figure. I would add if I were chief of the service in a major teaching hospital and if I could not get my residents and internes to do better than that, I think that maybe I would look at myself, not my staff.

I think we can do better than that. I think maybe some do better than this, but I think the situation is generally poor throughout the country.

Senator MCINTYRE. Mr. Chairman, you asked the question back there, or called for the figures on the number of reports that FDA had received on thromboembolic disease and deaths (6791)
associated with the pill, and I just want to make sure the answer you gave includes all reports which have been received

by FDA from all sources since these drugs came on the market. And if your answer was not inclusive as far as that is concerned, would you please supply it for the record? Do I make myself clear?

Dr. EDWARDS. Yes, I believe they were, were they not?

Senator JENNINGS. No, they were not, and that is what I pointed out to the Senator and said we would compile the figures I think he wants.

Dr. EDWARDS. I was thinking of something else.

Senator MCINTYRE. We had a feeling the figures you gave in response to the chairman's questions were only partial and I wanted to make sure.

Dr. EDWARDS. The period was from July to December, 1969. We will give you the total compilation of the figures.

Senator MCINTYRE. Thank you very much.

Dr. EDWARDS. Again, referring to the letter that the Food and Drug Administration sent to all physicians in 1968, the letter expressed the Food and Drug Administration's conclusion that a definite association had been established—this is between the oral contraceptive and thromboembolic disease, and called their attention to the revised labeling, and asked for their assistance in monitoring adverse reactions.

In 1969, FDA's OB-GYN committee made another comprehensive review of the oral contraceptive problem.

The second report was published on August 1, 1969. In addition to a comprehensive review of the problem, the report contained the results of a well-defined retrospective study on thromboembolic phenomena by Dr. Philip E. Sartwell of Johns Hopkins. The Sartwell study established the association of increased risk of some thromboembolic disorders, confirming the earlier British studies.

Although the committee had also studied the problems relating to carcinogenesis and metabolic effects, they could not

point to conclusive evidence associating these conditions with the use of oral contraceptives.

The committee concluded that "When these potential hazards and the value of the drugs are balanced, the ratio of benefit to risk is sufficiently high to justify the designation safe within the intent of the legislation."

As in their first report, the committee made a number of recommendations.

First of all, they recommended we investigate the carcinogenic and metabolic effect of oral contraceptives in humans.

They recommended we support development of new methods of contraception.

They recommended we support the National Fertility Survey in 1970 by the National Institute of Health.

They recommended that we improve the present system of reporting adverse reaction by financially supporting the use of centers to report reactions on oral contraceptives and by strengthening the present surveillance system of the Food and Drug Administration. (6792)

Lastly, they recommended that we sponsor an annual conference of scientific writers on contraceptive knowledge and accomplishments.

The FDA's review of the committee report and the Sartwell study led to a decision that a change in the uniform labeling was necessary. Accordingly, on November 14, 1969, we met with industry representatives to discuss the revised uniform labeling which has been required since January 1 of this year.

In December when I became Commissioner, the decision was made to issue a letter to all U.S. physicians, hospital pharmacists, and hospital administrators. In it, I warned that "carefully designed retrospective studies show that users of oral contraceptives are more likely to have thrombophlebitis and pulmonary embolism than nonusers" and I strongly urged physicians to familiarize themselves with the revised labeling.

I suggested that "a full disclosure of the potential adverse effects" to patients is advisable, and I also again requested their assistance in reporting adverse reactions to the Food and Drug Administration.

In addition, in December of 1969, reports came to our attention of the British announcement advising practitioners to prescribe only products containing .05 milligrams or less of estrogen. I indicated then that the Food and Drug Administration would await full data from England and evaluate this and our own data before making a decision on whether any action should be taken with regard to the oral contraceptives containing high doses of estrogen.

I would like to say in this regard, we just yesterday or the day before received a message from the British, inviting us to come to London on March 18 with appropriate individuals from the Food and Drug Administration and the National Institute of Health, to review their data.

So this month we will have the British information.

Senator NELSON. You will be sending a delegation shortly, did I understand you to say?

Dr. EDWARDS. That is right. We are to be there on March 18.

Senator NELSON. Are you, as Commissioner, going with the delegation?

Dr. EDWARDS. Yes, sir, I am. Three people from the Food and Drug Administration, in addition to two from the National Institute of Health.

Senator NELSON. If their data satisfies you and the group with you that oral contraceptives with more than 50 micrograms of estrogen do in fact induce a higher incidence of thromboembolism, will it be the decision of the FDA to order from the market all of those in this country that exceed 50 micrograms?

Dr. EDWARDS. Obviously, I think it would depend to a certain degree on the quality, or at least our interpretation of the quality of their data.

I think we have to continually bear in mind the formulation of these products, and this is certainly one of the alternatives that we have to think about if the data warrant it such a decision.

Senator NELSON. That is what I am getting at. If you and your scientists are satisfied with the quality of the research and conclude that they are correct, that over 50 micrograms increases the incidence of thromboembolism, would you be (6793)
inclined then to order from the market all of our oral contraceptives that exceed that?

Dr. EDWARDS. Again, I think we would have to give this very serious consideration. If the data were of the quality that we insist upon in the studies that we currently have ongoing in this country, I think we would have to consider this, yes.

Senator NELSON. Is there any question of the effectiveness of the 50 microgram tablet—I am not talking about the side effects—the effectiveness in preventing pregnancy, inhibiting ovulation?

Dr. EDWARDS. I would like to have Dr. Jennings answer that question, if I may. I think he perhaps is a little more familiar with it.

Dr. JENNINGS. I think that the picture is perhaps not quite as simple as simply a difference between .05 milligrams of estrogen and .08 milligrams. The two commonly used estrogens are ethinyl estradiol, which is usually present in a quantity of .05 milligrams, and mestranol, which is usually present in the higher dosage.

Both of these seem to be effective at those respective levels. There was some indication that a lesser amount of mestranol, the one that is usually present in the higher amount, might not be as effective as manifested by breakthrough bleeding, I believe, and also by pregnancy rates in some of the studies where this amount was lowered.

So I think that in addition to simply considering the two levels of estrogen, a certain difference in the estrogenic strength of the two products, the two compounds, has to be considered.

In addition, the products currently on the market all include progesterones, either to be taken in combination throughout the period of medication, or to be taken in sequence. The progesterones vary also in their estrogenic effect. So that this also has some bearing on the potential for the side effects that might be attributed to estrogenic activity.

I think all of this will have to be taken into consideration when the British data are available to us.

Senator NELSON. Thank you.

Senator MCINTYRE. Mr. Chairman, a question. I would like to know if you have received any of the British data as of now.

Dr. EDWARDS. No.

Senator MCINTYRE. Thank you.

Dr. EDWARDS. I think with all due respect, it is a matter of their not having been able to tabulate their information. I think it has been rather substantial. And I think they have had trouble pulling it all together. It has not been because they have been trying to keep it from us, it is just they wanted to get it in order before we had an opportunity to look at it.

Senator MCINTYRE. Thank you.

Dr. EDWARDS. Another action taken soon after I became Commissioner was to convene a meeting of our OB-GYN Advisory Committee. I met with this group on January 21 to re-evaluate available information on oral contraceptives. I believe the advice and counsel of this group is important to our work in this area, and I intend to meet with them every 30 to 60 days.

I think this is perhaps an appropriate occasion to announce that Dr. Allan C. Barnes, professor and chairman of the Department of Obstetrics and Gynecology at John Hopkins University is the new chairman of our advisory committee, replacing Dr. Hellman. (6794)

Dr. Barnes will chair our meeting next Wednesday when we will review some of our present research projects.

I would like at this time to review some of our studies which are now under way. There are several general areas on which the total scope of the Food and Drug Administration's present program is based.

Information is being sought on the degree and mechanism of changes brought about by the oral contraceptive and the indications of these changes.

Also, we are trying to determine whether certain of these drugs, or their ingredients, have unique pharmacological properties; whether high risk subpopulations can be identified; and to what degree can findings observed in animals be extrapolated to the human population.

Clinical and animal studies presently under way and supported by the Food and Drug Administration include:

A retrospective study of a cost of $175,000 on the relationship between thromboembolic phenomena and oral contraceptive use conducted by Dr. Philip Sartwell at the Johns Hopkins University School of Hygiene and Public Health. Here we are planning to extend this for another year, beginning next month, at a cost of approximately $75,000.

We have an investigation going on of the carcinogenic potential, hematologic, and endocrine effects of two experimental oral contraceptive formulations using dogs and monkeys treated over a prolonged period of time. This continuing study by the International Research and Development Corp., was begun late in 1968 at a cost of $372,000.

We have an intensive study of changes in blood cogulation and fibrinolysis in women using oral contraceptives, which was initiated at the New York University School of Medicine in May 1969, at an annual cost of $27,000. Results are expected early in 1971.

We have the study of the University of Rochester on the possible effects in women of oral contraceptives on renal, bladder and ureteral function and the incidence of infection which was initiated in May 1969, at an annual cost of $77,000.

We have the study at Temple University on the effects of oral contraceptives on lipid metabolism in subhuman primates and women of reproductive age, which was initiated in May of 1968 at an annual cost of $118,000.

We have a prospective study on the effects of prolonged use of oral contraceptives on carbohydrate metabolism in a large group of women, and this has been underway at the University of Miami since June 1967, at annual cost of $63,000.

Lastly, we have a study at Temple University on the effects of oral contraceptives on cervical cytology which was initiated in July of 1969 at a cost of $95,000.

All of these studies are currently costing the Food and Drug Administration $380,000 annually.

Senator DOLE. Dr. Edwards, there has been some testimony that additional funds are needed to research oral contraceptive research. Do you feel additional funds are needed, and if so, in what specific areas? (6795)

Dr. EDWARDS. I think without any hesitation I would say that our research efforts in this whole general field have to be increased, both within the Food and Drug Administration and at the National Institute of Health.

Senator DOLE. You indicated on page 10 an increase of $700,000 to in excess of $3 million.

Dr. EDWARDS. When I say the 3 million, I am talking a ballpark figure and I am talking about total research. Again I do not mean that we are capable of taking this kind of increase all at once, but I think over a period of several years. I think this is the ballpark figure that we are talking about.

Senator DOLE. There are specific areas now with reference to oral contraceptives, where research could be done if you had the money, is that your opinion?

Dr. EDWARDS. I think additional research needs to be done in a number of these areas. This whole area of the carbohydrate metabolism, lipid metabolism, the possible effect or rela-

tionship between the oral contraceptive and carcinogenic effects have to be looked into in much greater depth than we have at this point in time. I am speaking only for the Food and Drug Administration, of course. Our research funds are extremely limited, and we have had to establish priorities. And as I can assure you, in establishing these priorities, the oral contraceptives have been up at the top of our list. So we have spent most of our funds on research in the oral contraceptives.

There are other areas, but I think these are certainly some of the main areas where additional research needs to be done.

Senator DOLE. Thank you

Senator NELSON. May I pursue that subject a little further?

I guess every witness has commented on the question, including General Draper and Dr. Guttmacher, as well as various physicians and specialists who have appeared before the committee. They have all deplored the lack of adequate amounts of research. One of the points raised, I think by Dr. Corfman of NIH, although the record will correct me if it were not he, was that unfortunately there has been no dosage level research done in terms of trying to find out how low a dosage of progesterones and estrogens may be given and still be effective and what reduction in incidence of side effects might occur as a consequence of lower dosages or lower dosages in various combinations.

And you know, of course, that the first pills were 150 micorgrams of estrogen and were effective, and 100 were effective, and 75 were effective. The British seem to think 50 are effective.

Would you consider it an important piece of research to establish some protocol for comprehensive investigation of this aspect of the oral contraceptive?

Dr. EDWARDS. Very definitely. I think this is an area in which far too little has been done. I am thinking in terms of the formulation of these products, the minimum amount that will provide the efficacy that we want.

I think some of this, however, has to also be done by the industry. And who does what is a rather difficult question for me. The answer is a difficult one. But I think without any question this is an area I should have mentioned in greater detail. I think much more has to be done, and I think we have to play an important role in stimulating this research, either we do it or we stimulate industry to do it. (6796)

But I think without any question this is one of the most important areas.

Senator NELSON. Again, this is a legal question: What authority does the FDA have to require drug companies to do additional research after a drug has been placed on the market? In this case dose level studies?

Do you have authority to require such data?

Dr. EDWARDS. I would like to have Mr. Goodrich answer that. I am not sure about our authority, but after all, in approving new drugs, we have to evaluate and judge the adequacy of the clinical investigations that have led up to the marketing of this drug, and in our judgment, if these are not adequate, then I think we certainly can go back to that particular company and say more study needs to be done in these particular areas; but legally, I would like to turn to Mr. Goodrich.

Mr. GOODRICH. Our legal authority is to require the companies to make either a regular or special report. A report could be called for on any phase of the safety decision. If we attempt to require the research, our ultimate administrative step would be to withdraw approval.

We have legal authority to withdraw approval at any time we find that there is a lack of adequate evidence, either of safety or of effectiveness.

So what would have to be done would be to identify with the company those areas in which additional research was needed, some kind of time within which this could be done, and say that if it were not done, they would be risking the loss of the product by the withdrawal of approval.

We do not have any direct authority to say do this research, but the ultimate withdrawal possibility does facilitate a good deal of research.

Senator NELSON. In the specific case at hand, or with any drug, a potent one, anyway, extensive use over a period of years develops information that could not have been developed by FDA, so you have a case here where where thromboembolism was proven quite early, and statistics have accumulated to support it.

Do you have the authority to say it is pretty clear that a drug could be developed with less dramatic side effects, a lower incidence, therefore you must proceed with some protocol for investigating this possibility?

Mr. GOODRICH. We think so. But as I say, our ultimate, if they refuse to do it, our ultimate step would have to be to withdraw approval.

Senator NELSON. I understand.

I would like to ask another question in the research field. This concerns the report based on the workshop sponsored by NIH on "Metabolic Effects of Gonadal Hormone and Contraceptive Steroids." In the preface on page 9, I quote: (6797)

> Until recently, the metabolic effects of the contraceptive steroids have been inadequately investigated or ignored. These accumulated data and other suggest that no tissue or organ system is * * * a biological function and/or more * * * effect of contraceptive steroids. Many of these changes appear to be reversible after short periods of treatment. But it is impossible to form judgments on the reversibility of some of the changes resulting from prolonged administration. This question becomes more important daily for the many patients who already had long-term contraceptive steriod treatment.

It seems to me this raises a very serious question, since we really do not know what the consequences of these metabolic changes are over a long period of time.

My question is: Are you satisfied that we are doing enough research on this aspect of the problem, and if not, do you have some view about what we ought to be doing?

Dr. EDWARDS. By "this aspect of the problem," you are referring to the time period over which the oral contraceptive is given a particular patient; right?

Senator NELSON. And the metabolic effects of it.

Dr. EDWARDS. And the permanent effects this might have on the patient's metabolic system, et cetera.

I share with you concern about this, and certainly I think this is an area that we have to look at very seriously, along with groups at the National Institute. I have personal reservations about allowing the oral contraceptive to be given over indefinite periods of time. I have no knowledge of scientific evidence at the moment that would substantiate this view, but I think that some of the retrospective and prospective studies we are proposing or actually have in progress at the moment will help answer some of these questions. But it is a very serious subject of concern and I think it is one I hope our advisory group will address themselves to this next week.

Senator NELSON. That is the question of extended administration without interruption?

Dr. EDWARDS. Right, and what kind of studies would best allow us to make some scientific judgment on the advisability of this, or what is the ideal length of time over which one of the oral contraceptives can be given.

Senator NELSON. As you know, we have had a number of witnesses who have expressed their opinion, again without having the proof, as you said, who had reservations such as you have indicated you have.

One of the witnesses said that he would not want to have it used more than 2 or 3 years continuously without interruption.

Others expressed a similar viewpoint about long-term usage, simply because we do not have the studies that would

indicate whether or not the metabolic changes that are effectuated on account of the administration of the pill have any long-term damaging effects.

Do I understand you to say that the new committee being constituted now on obstetrics and gynecology will address itself to the question of length of time the drug should be administered?

Dr. EDWARDS. I think there are a number of areas that we would like to have them address their attention to, but this certainly is one of the areas that should receive a high priority on the agenda of the committee. (6798)

To complete the review of our studies in which we are indirectly involved, I will mention that we have participated in the monitoring of the prospective study of oral contraceptive users being conducted under support from the National Institute of Child Health and Development at the Kaiser Permanente Foundation in Walnut Creek, Calif.

In addition, we have participated in the review of two planned retrospective studies relating to the possible effects of oral contraceptives on carcinoma of the breast submitted to and approved by the National Institute of Child Health and Development. Funding for these studies has not yet been approved.

This investment in research, in our judgment, is necessary to better define the hazards of the oral contraceptive.

The questions of safety must be answered in so far as is possible for science to find the answers. And we at the Food and Drug Administration must continuously review our previous decisions in light of new scientific knowledge.

We have plans underway to develop other studies. These include the effect of oral contraceptive drugs in prediabetic and diabetic patients: cytogenetic studies in spontaneous and induced abortions; development of other techniques to assess the effects of oral contraceptives on endocrine function during adolescence; and the metabolism of the hormonal contraceptives and possible interaction with other drugs.

In order to get these studies under way, it will require an increase in our current research budget from approximately $700,000 in fiscal year 1970, to over $3 million.

I would like to turn to another subject which will require very substantial funding if we are to do an effective job. This is the need for a comprehensive drug surveillance system.

Because of the limited nature of premarketing clinical trials, we cannot expect to observe all of the adverse reactions that may occur. We are dealing with comparatively small numbers of patients who are screened carefully and regularly. The difficulty of detecting adverse reactions is great. Our statisticians tell us that an adverse reaction expected to occur at a rate of 1 in every 1,000 will not be observed at all in 37 percent of studies using 1,000 subjects. In other words, to be 97 percent certain of observing such a high rate of adverse reaction, a study would need to include 10,000 or more subjects.

Therefore, it is essential that all approved drugs be kept under close surveillance through an effective adverse reaction reporting system. At present this system in the United States depends for the most part on voluntary submission of adverse reactions by physicians and hospitals and, of course, the required reports from the drug manufacturers. It is unfortunate, but true, that we receive reports on only a small percentage of the total number of adverse reactions that occur. This limited access to the medical record makes it extremely difficult to evaluate cause and effect. We must move in the direction of significantly improving our surveillance system. I would estimate it would take at least a third of our present budget to establish such a comprehensive reporting system.

Senator NELSON. Would this be compulsory? (6799)

Dr. EDWARDS. No. At least we are not in any position at this point to make reporting compulsory. But I think with the right kind of a system, a computerized system, where the medical record is far more computerized than it is at the present time would be helpful. I do not think it would have to be a compulso-

ry system to get a reasonably good response in terms of drug reporting.

Senator NELSON. We had that, of course, in some of the communicable diseases.

Dr. EDWARDS. I think though that for this, Senator Nelson, for this to be effective, really an effective reporting system, we are eventually going to have to get the record out of the doctor's office. Obviously this is where some of the minor reactions occur and it is not just the hospital record.

I think the time is coming when we will have a medical record that is automated, a centralized medical record, if you will. When this happens, I do not believe it will be a matter of whether reporting will be compulsory or noncompulsory, it will be on the record.

And I think all of this is within the realm of possibility.

Senator NELSON. I must say, in looking at one of the reports submitted to the physician by the FDA, the number of questions and the fine lines, that it is a kind of discouraging thing for the physician to fill out. As you know, all Federal forms somehow or another get to be enormously detailed. It might help, I suppose, if there were some way to simplify it.

Dr. EDWARDS. I suspect you are correct, and I have not had an opportunity to look at the system that we use, but I am certain that what you say is true.

And I think in terms of developing an adverse reporting system, we have to look at what the FDA requires, as well as what the system provides generally. So we will be looking at out capabilities in this regard, too.

Senator NELSON. Thank you.

Dr. EDWARDS. Under the present system we try to keep the physician abreast of adverse reactions as we become award of them. This is certainly true with regard to the oral contraceptives. There is no question that it is vitally important to communicate this information to the physician, but there is also

corresponding need to keep the patient well informed. I believe that the patient should receive as much accurate information as is necessary for her to make certain decisions.

Let me examine for just a moment how women are currently being informed as regards the oral contraceptive.

They get a good deal of information and misinformation from sources other than the physician—through newspapers, pamphlets, books, television, and from discussion with others. This additional information is reaching a large number of people in a short period of time. While we can control the prescribing information which goes to the physician and any printed or graphic matter that may ultimately reach the patient through him, we have no such opportunity to see that other presentations are accurate, balanced, and properly informative. (6800)

I have come to the conclusion that the information being supplied to the patient in the case of the oral contraceptive is insufficient and that a reevaluation of our present policies is in order.

Accordingly, I have asked our Bureau of Drugs to examine this area of consumer information and to give me their recommendations.

I have with me today, which I will submit to you, a statement which we are going to publish in the Federal Register so that all interested parties will have an opportunity to comment on it. This statement is the proposed language for a reminder leaflet of uniform content which will be placed by the manufacturer into each package of oral contraceptives produced.

This leaflet is designed to reinforce the information provided the patient by her physician. I emphasize the word "reminder" as its purpose is to recall to the patient her discussion with the physician when she made her decision to begin taking an oral contraceptive.

I will not read this unless you would like.

(The statement follows:)

WHAT YOU SHOULD KNOW ABOUT BIRTH CONTROL PILLS

(ORAL CONTRACEPTIVE PRODUCTS)

All of the oral contraceptive pills are highly effective for preventing pregnancy, when taken according to the approved directions. Your doctor has taken your medical history and has given you a careful physical examination. He has discussed with you the risks of oral contraceptives, and has decided that you can take this drug safely.

This leaflet is your reminder of what your doctor has told you. Keep it handy and talk to him if you think you are experiencing any of the conditions you find described.

A WARNING ABOUT "BLOOD CLOTS"

There is a definite association between blood-clotting disorders and the use of oral contraceptives. The risk of this complication is six times higher for users than for non-users. The majority of blood-clotting disorders are not fatal. The estimated death rate from blood-clotting in women *not* taking the pill is one in 200,000 each year; for users, the death rate is about six in 200,000. Women who have or who have had blood clots in the legs, lung, or brain should not take this drug. You should stop taking it and call your doctor immediately if you develop severe leg or chest pain, if you cough up blood, if you experience sudden and severe headaches, or if you cannot see clearly.

WHO SHOULD NOT TAKE BIRTH CONTROL PILLS

Besides women who have or who have had blood clots, other women who should not use oral contraceptives are those who have serious liver disease, cancer of the breast or certain other cancers, and vaginal bleeding of unknown cause.

SPECIAL PROBLEMS

If you have heart or kidney disease, asthma, high blood pressure, diabetes, epilepsy, fibroids of the uterus, migraine

headaches, or if you have had any problems with mental depression, your doctor has indicated you need special supervision while taking oral contraceptives. Even if you don't have special problems, he will want to see you regularly to check your blood pressure, examine your breasts, and make certain other tests.

When you take the pill as directed, you should have your period each month. If you miss a period, and if you are sure you have been taking the pill as directed, continue your schedule. If you have not been taking the pill as directed and if you miss one period, stop taking it and call your doctor. If you miss two periods, see your doctor even though you have been taking the pill as directed. When you stop taking the pill, your periods may be irregular for some time. During this time you may have trouble becoming pregnant. (6801)

If you have had a baby which you are breast feeding, you should know that if you start taking the pill its hormones are in your milk. The pill may also cause a disease in your milk flow. After you have had a baby, check with your doctor before starting to take oral contraceptives again.

WHAT TO EXPECT

Oral contraceptives normally produce certain reactions which are more frequent the first few weeks after you start taking them. You may notice unexpected bleeding or spotting and experience changes in your period. Your breasts may feel tender, look larger, and discharge slightly. Some women gain weight while others lose it. You may also have episodes of nausea and vomiting. You may notice a darkening of the skin in certain areas.

OTHER REACTIONS TO ORAL CONTRACEPTIVES

In addition to blood clots, other reactions produced by the pill may be serious. These include mental depression, swelling, skin rash, jaundice or yellow pigment in your eyes, increase in blood pressure, and increase in the sugar content of your blood similar to that seen in diabetes.

POSSIBLE REACTIONS

Women taking the pill have reported headaches, nervousness, dizziness, fatigue, and backache. Changes in appetite and sex drive, pain when urinating, growth of more body hair, loss of scalp hair, and nervousness and irritability before the period also have been reported. These reactions may or may not be directly related to the pill.

NOTE ABOUT CANCER

Scientists know the hormones in the pill (estrogen and progestrone) have caused cancer in animals, but they have no proof that the pill causes cancer in humans. Because your doctor knows this, he will want to examine you regularly.

REMEMBER

While you are taking ____, call your doctor promptly if you notice any unusual change in your health. Have regular checkups and your doctor's approval for a new prescription.

Senator NELSON. I would appreciate it if you would read it. I have not read it yet. I might have a question.

Dr. EDWARDS. I might read the first page and then summarize the rest of it and any of the technical matter. The title of this is "What You Should Know About Birth Control Pills."

> All of the oral contraceptive pills are highly effective for preventing pregnancy, when taken according to the approved directions. Your doctor has taken your medical history and has given you the risks of oral contraceptives, and has decided that you can take this drug safely.
>
> This leaflet is your reminder of what your doctor has told you. Keep it handy and talk to him if you think you are experiencing any of the conditions you find described.

Then the next section is a warning about blood clots. Here we indicate there is a definite association between bloodclotting disorders and the use of oral contraceptives. The risk of this

complication is six times higher for users than for nonusers. And although the majority of blood-clotting disorders are not fatal, the estimated death rate from blood clotting in women not taking the pill is 1 in 200,000 each year. For the user, the death rate is about 6 in 200,000. (6802)

Women who have blood clots in the legs, lungs or brain, should not take this drug. You should stop taking it and call your doctor immediately if you develop severe leg or chest pain, if you cough up blood, if you experience sudden or severe headaches, or if you cannot see clearly.

Senator NELSON. The figures that have been used frequently before the committee indicate that hospitalization from blood clotting occurs in 1 of every 2,000 users. Is there any reason for not using that figure in here?

Dr. JENNINGS. I think, Senator, there are any number of ways we could express this. All the data we have on this particular phenomenon, both morbidity and mortality, are somewhat inexact. I think what we attempted to do here was zero in on the most serious aspect of this, and to give the woman some idea of the magnitude of the problem.

In other words, it would not be enough for her to know that the rate was increased for users by a certain number, four to nine times, unless she had some idea of magnitude; one in a thousand multiplied by four to nine times would be a large number.

One in 200,000 multiplied approximately six or four to nine would be a much smaller number. And I think that is what we are trying to get across here, that there is an increased risk among users compared to nonusers and that for the most serious result of this complication, the fatality, occurs in this order of frequency.

Senator NELSON. I notice that in the Dear Doctor letter of June 28, 1968, which included the package insert, the hospitalization rates of morbidity age 20 to 24, it is 47 per 100,000. If I interpret this correctly, you have the hospitalization rate of almost one in 2,000. Am I interpreting it correctly?

Dr. JENNINGS. Yes, I think that would be one way of putting it. That was ahospitalization rate, which is one indication of morbidity. I think what we attempted to do here was not a literal translation of the information given to the physician, who is, after all, much more sophisticated and capable of handling these numbers, but to try in a simple fashion to alert the woman to the fact that there was an increased risk and then to give her some idea of the magnitude of this, especially in relation to the most important, that is, the fatality.

Senator NELSON. Well, all I say, as just a layman reading it, is that when you talk about the death rate being one in 200,000 for women not taking the pill and for users six in 200,000, those are very large figures. But when you get down to the more practical aspect in a higher incidence and talk about almost one in 2,000 being hospitalized, which is a very high incidence, it is a figure that is much easier to understand, and does not just talk about deaths, it talks about hospitalization rates.

I just raise the question because it seems to me, a very significant statistic to include. If I were a patient, I would want to know that one in 200,000 die who were not taking the pill and six in 200,000 do who are taking it, and I might say to myself, well, that six out of 200,000 is very low.

On the other hand, if you would say one out of 2,000 is going to be hospitalized by blood clots alone, that is a pretty dramatic (6803)
figure, and I would think it is one that is quite understandable and ought to be used.

Dr. EDWARDS. I think your point is well taken, and I would emphasize that this is not the final package. This is for discussion purposes primarily, and we certainly anticipate making changes, as requested by groups such as your committee and others.

I think your particular point is a good one.

Senator DOLE. Dr. Edwards, this insert has been in the making for sometime; is that correct?

DR. EDWARDS. Right.

Senator DOLE. I am not certain whether the average person realizes there is any great risk if it is one out of 200,000 or six out of 200,000. We have had witnesses indicate we should not include a laundry list with medication, because to do so would confuse the patient.

I am not certain where you draw the line, whether you should indicate any numbers, whether you should indicate there is some risk. The question is how to best communicate with patients, but we do not want to frighten the few people left who are not frightened as a result of these hearings.

I would hope that we do not try to rewrite the memorandum in committee hearing.

Senator NELSON. I hope the Commissioner did not think I was trying to rewrite the memorandum; I was just asking the question for information purposes because I thought it was a good question. I would not think of trying to write the memorandum, but I would think it is within the province of a member of the committee or any citizen in America, and there are 200 million of them, to ask a question.

Senator DOLE. We have asked several questions.

Dr. EDWARDS. Certainly our intent is not to frighten anyone away from the pill, but it is our intent to prepare a document, and as I say, I will not stand on this particular document, but prepare a document that gives the facts in an unemotional way so that the many, many patients in this country who are receiving the oral contraceptive by renewal of prescriptions, et cetera, will at least have some access to appropriate information.

Senator DOLE. Will this be an additional piece of information, in addition to what the drugmaker himself may include? Are we going to have two pieces of literature to read, or does this supersede anything else?

Dr. EDWARDS. I believe I am correct—Dr. Jennings can correct me—that at the present time there are no inserts in these packages per se, are there?

Dr. JENNINGS. No, there are not.

Dr. EDWARDS. Except for the physician.

Dr. JENNINGS. That is right. But I think the Senator is referring to the booklets that are frequently prepared.

Senator DOLE. Right.

Dr. JENNINGS. For patient use.

Senator DOLE. You have one entitled "So Close to Nature" which we had last week.

APPENDIX C

FDA's "Dear Doctor" Letter Of June 28, 1968, And Revised Uniform Labeling For Oral Contraceptives

APPENDIX C

DEPARTMENT OF HEA' TH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,

Washington, D.C., June 28, 1968.

DEAR DOCTOR: Since 1960, when the first oral contraceptive was marketed in the United States, these drugs have been prescribed in a volume which may exceed that of any other potent medication. According to current estimates, more than six million American women now use oral contraceptives. As the drugs have been used more widely, adverse reactions, not known at the time of original Food and Drug Administration approval, have become evident; the labeling of the drugs has been revised from time to time to include this new knowledge.

The most recent data developed in studies conducted in Great Britain confirms what had been suspected: *there is a definite association between the use of oral contraceptives and the incidence of thromboembolic disorders.* New labeling, which will be in use by July 1, 1968, contains excerpts from the British reports and appropriate revisions of prescribing information. The labeling is uniform for all drugs in this class, and is in the standard format recommended by the FDA for all drug labeling.

A copy of the revised uniform labeling is attached. We urge you to give careful consideration to the information under the various cautionary headings in the labeling.

We ask, too, for your assistance in monitoring adverse reactions by reporting all such reactions to the Food and Drug Administration. A supply of the standard reporting form (FD 1639), shown in facsimile on the reverse of this letter, may be obtained by writing to: Bureau of Medicine, Food and Drug Administration, Washington, D.C. 20204.

Sincerely yours,

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs.

Attachment:

Revised uniform labeling

Uniform Section of Oral Contraceptive Labeling

Chemistry

This should include generic name, amount, chemical name and the structural formula of each active ingredient.

Mechanism of Action

(As presented in current package insert.)

Indications

The Obstetrics and Gynecology Advisory Committee considered the following indications acceptable: contraception, endometriosis, and hypermenorrhea. These indications may be used in the labeling when efficacy has been demonstrated in each case. Any other claims will be evaluated on the basis of efficacy data available to support each.

Contraindications

1. Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions.

2. Patients with markedly impaired liver function.

3. Patients with known or suspected carcinoma of the breast.

4. Patients with known or suspected estrogen dependent neoplasia.

5. Undiagnosed abnormal genital bleeding.

Warnings

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Studies conducted in Great Britain and reported in April 1968 [1,2] estimate there is a seven to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

COMPARISON OF MORTALITY AND HOSPITALIZATION RATES DUE TO THROMBOEMBOLIC DISEASE IN USERS AND NON-USERS OF ORAL CONTRACEPTIVES IN BRITAIN

Category	Mortality Rates		Hospitalization rates (morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of oral contraceptives	1.5/100,000	3.9/100,000	47/100,000
Nonusers	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be directly applied to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may be different.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

3. Since the safety of * * * in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out

[1] Inman, W.H.W. and M. P. Vessey, British Medical Journal 2:193-199, 1968.

[2] Vessey, M. P. and R. Doll, British Medical Journal, 2:199-205, 1968.

before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear.

2. Endocrine and possibly liver function tests may be affected by treatment with * * *. There, if such tests are abnormal in a patient taking * * *, it is recommended that they be repeated after the drug has been withdrawn for 2 months.

3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size.

4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginum, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginum, adequate diagnostic measures are indicated.

6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

7. Any possible influence of prolonged * * * therapy on pituitary, ovarian, adrenal,hepatic or uterine function awaits further study.

8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The

mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving * * * therapy.

9. Because of the effects of estrogens on epiphyseal closure * * * should be used judiciously in young patients in whom bone growth is not complete.

10. The age of the patient constitutes no absolute limiting factor, although treatment with * * * may mask the onset of the climacteric.

11. The pathologist should be advised of * * * therapy when relevant specimens are submitted.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis	Pulmonary embolism

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Cerebrovascular accidents	Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives (Consult the clinical section.)

Nausea	Change in weight (increase or decrease)
Vomiting	Changes in cervical erosion and cervical secretions

- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea during and after treatment
- Edema
- Chloasma or melasma
- Breast changes: tenderness, enlargement and secretion
- Suppression of lactation when given immediately post-partum
- Chloestatic Jaundice
- Migraine
- Rash (Allergic)
- Rise in blood pressure in susceptible individuals
- Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

- Anovulation post treatment
- Prementrual-like syndrome
- Changes in libido
- Changes in appetite
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Fatigue
- Backache
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Itching

The following laboratory results may be altered by the use of oral contraceptives (see sections on clinical laboratory):

- Hepatic functions: Increased sulfobromophthalein and other tests
- Coagulation tests: increase in prothrombin Factors VII, VIII, IX and X
- Thyroid functions: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 values
- Metryapone test
- Pregnanediol determination

Animal Studies

This should include results of acute, chronic toxicity and reproduction studies using the compounds present in the product. Significant laboratory and pathologic findings should be mentioned.

Endocrine and metabolic screening. State results on dose per weight basis.

Clinical Data

Efficacy—This should include the number of cycles completed. Breakdown by number of patients completing a specific number of cycles should also be mentioned. State number of pregnancies in number per 100 woman years. Pearl's formula or life table technique should be used. The following statement is permitted if applicable: "Virtually 100% effective when used according to directions."

Adverse Reactions Clinical Laboratory Results—This should include liver, thyroid, renal functions, coagulation tests, endocrine function as well as routine hematology and cytology.

Dosage And Administration

This should include routine administration and specific instructions on handling problems such as breakthrough bleeding, amenorrhea, etc.

Availability

Bibliography

Reference, not a complete bibliography.

May 10, 1968 / Food and Drug Administration / U.S. Department of Health, Education, and Welfare / Washington, D.C. 20204.

APPENDIX D

FDA's "Dear Doctor" Letter Of January 12, 1970, And Revised Uniform Labeling For Oral Contraceptives

APPENDIX D

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,

Washington, D.C., January 12, 1970.

DEAR DOCTOR: I am enclosing revised labeling for oral contraceptives to reflect the latest findings on safety and efficacy, as reported by the Obstetrics and Gynecology Advisory Committee in August 1969. An American study confirms previously reported studies in Great Britain which show a relationship between the use of oral contraceptives and the occurrence of certain thromboembolic diseases. These carefully designed retrospective studies show that users of oral contraceptives are more likely to have thrombophlebitis and pulmonary embolism than non-users. Studies in Great Britain also show increased risk of cerebral thrombosis and embolism in users of oral contraceptives. A British study found a hospitalization rate (an index of morbidity) in women age 20-44 to be 47 per 100,000 in users compared to five per 100,000 in non-users.

The American study, although not designed to evaluate differences between products, also suggests there may be an increased risk of thromboembolic disease in users of sequential products. This difference in risk cannot be quantitated, and further studies are needed to confirm the observation.

The British Committee on Safety of Drugs recently advised practitioners in that country that only products containing 0.05 mg. or less of estrogen should normally be prescribed because reports of suspected adverse reactions indicated there is a higher incidence of thromboembolic disorders with products containing 0.075 mg. or more of estrogen than with products containing the smaller dose. This finding has not been confirmed by other studies.

The FDA is planning studies that will determine, among other things, the thromboembolic effect of various products. You will be kept informed as results become available.

Other aspects being investigated in separate studies underway or pending are cervical cytology, carbohydrate metabolism, serum lipids, urinary tract function, blood coagulation, effects on endocrine function in adolescents, breast pathology, outcome of pregnancy, and cytogenetic effects.

In the United States during 1969 an estimated 8.5 million women took oral contraceptives monthly. The unsurpassed clinical efficacy of these products is well established. Although reported pregnancy rates vary from product to product, the effectiveness of sequential products appears to be somewhat lower than that of the combination products.

I strongly urge you to familiarize yourself with the labeling, particularly with the cautionary material contained in the sections headed Contraindications, Warnings, Precautions, and Adverse Reactions. As the prescribing physician, you are in the best position to determine the extent of your discussion of this material with your patient. In most cases, a full disclosure of the potential adverse effects of these products would seem advisable, thus permitting the participation of the patient in the assessment of the risk associated with this method.

I also request your assistance in continuing our assessment of the safety of oral contraceptives. Your reports of adverse reactions will help us to do this. A supply of the standard reporting form (FD 1639), shown in facsimile below, may be obtained from the Bureau of Medicine, Food and Drug Administration, Washington, D.C. 20204.

Sincerely yours,

CHARLES C. EDWARDS, M.D.,
Acting Commissioner of Food and Drugs.

Attachment:
Revised labeling

Oral Contraceptive Labeling

Description

This section includes generic name, amount, chemical name and the structural formula of each active ingredient.

Actions

Combination oral contraceptives: The mechanism of action is inhibition of ovulation resulting from gonadotropin suppression. Changes in cervical mucus and endometrium may be contributory mechanisms.

Sequential oral contraceptives: The mechanism of action is inhibition of ovulation resulting from gonadotropin suppression.

Special Note

Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision. Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS

The Obstetrics and Gynecology Advisory Committee considered the following indications acceptable: contraception, endometriosis, and hypermenorrhea. These indications may be used in the labeling when efficacy has been demonstrated in each case. Any other claims will be evaluated on the basis of efficacy data available to support each.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
2. Markedly impaired liver function.
3. Known or suspected carcinoma of the breast.
4. Known or suspected estrogen dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary emoblism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis and pulmonary embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country.

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[1] Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease. J. Coll. Gen. Pract., *13*:267-279. 1967.

[2] Inman, W.H.W. and Vessey, M. P. Investigation of Deaths from Pulmonary Coronary and Cerebral Thrombosis and Embolism in Women in Child Bearing Age, Brit Med J. *2*:193-199. 1968.

[3] Vessey, M. P. and Doll. R. Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit Med J, *2*:651-657, 1969.

[4] Sartwell, P. E., Masi. A. T., Arthes, F. G., Greene, G. R., and Smith, H. E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380, (November) 1969.

The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about seven fold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable. Retrospective studies in Great Britain have shown a statistically significant association between cerebral thrombosis and embolism and the use of oral contraceptives. This has not been confirmed in the United States.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

3. Since the safety of * * * in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.

2. Endocrine and possibly liver function tests may be affected by treatment with * * *. Therefore, if such tests are abnormal in a patient taking * * *, it is recommended that they be repeated after the drug has been withdrawn for 2 months.

3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size.

4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated.

6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

7. Any possible influence of prolonged * * * therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving * * * therapy.

9. The age of the patient constitutes no absolute limiting factor, although treatment with * * * may mask the onset of the climacteric.

10. The pathologist should be advised of * * * therapy when relevant specimens are submitted.

11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis

Cerebral thrombosis

Pulmonary embolism

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives:

Nausea

Vomiting

Gastrointestinal symptoms (such as abdominal cramps and bloating)

Breakthrough bleeding

Spotting

Change in menstrual flow

Amenorrhea during and after treatment

Edema

Chloasma or melasma

Breast changes: tenderness, enlargement and secretion

Change in weight (increase or decrease)

Changes in cervical erosion and cervical secretions

Suppression of lactation when given immediately post-partum

Cholestatic Jaundice

Migraine

Rash (Allergic)

Rise in blood pressure in susceptible individuals

Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

Anovulation post treatment	Fatigue
Premenstrual-like syndrome	Backache
Changes in libido	Hirsutism
Changes in appetite	Loss of scalp hair
Cystitis-like syndrome	Erythema multiforme
Headache	Erythema nodosum
Nervousness	Hemorrhagic eruption
Dizziness	Itching

The following laboratory results may be altered by the use of oral contraceptives:

Hepatic function: Increased sulfobromophthalein retention and other tests	Thyroid function: Increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values
Coagulation tests: Increase in prothrombin, Factors VII, VIII, IX, and X	Metayrapone test
	Pregnanediol determination

Dosage And Administration

This section includes routine administration and specific instructions on handling problems such as breakthrough bleeding, amenorrhea, etc.

Clinical Studies (An Optional Section)

If any clinical data are included, the following paragraph must be used: Different pregnancy and adverse reaction rates have been reported with the use of each oral contraceptive. Inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, pregnancy and adverse reaction rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and did not discontinue due to adverse reactions or pregnancy. In clinical trials with * * * patients completed * * * cycles, and a total of * * * pregnancies was reported. This represents a pregnancy rate of * * * per 100 woman years. Please see the SPECIAL NOTE in this labeling.